Human Research Program
Human Health Countermeasures Element

Evidence Book

Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity

Risk of Unnecessary Operational Limitations due to Inaccurate Assessment of Cardiovascular Performance

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I. Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity

Astronauts' physical performance during a mission, including activity in microgravity and fractional gravity, is critical to mission success. Setting minimum fitness standards and measuring whether crew can maintain these standards will document the effectiveness of maintenance regimens.

Risk of Unnecessary Operational Limitations due to Inaccurate Assessment of Cardiovascular Performance

Current inflight indicators of cardiac performance may not accurately reflect astronauts cardiovascular performance. Making operational decisions based on inaccurate cardiac performance measures may unnecessarily restrict crewmembers for critical activities or, more seriously, could subject crewmembers to activities for which they are not physically prepared. Accurate measurement of crewmember aerobic capacity can eliminate this risk.

II. Executive Summary

Maintenance of aerobic capacity during and after space flight is a significant concern to NASA. There is evidence that aerobic capacity is maintained during short-duration space flight, but that maximal exercise performance is impaired after landing, perhaps due to the combined effects of orthostatic stress and relative hypovolemia. Recent data from International Space Station (ISS) crewmembers participating in long-duration missions demonstrates that their heart rate responses to standard submaximal exercise intensities is increased, suggesting their maximal aerobic capacity is decreased, although this has not been directly measured. Decreased aerobic capacity during space flight is related to concomitant reductions in physical activity, plasma volume, erythrocyte mass, and muscular strength. Ground-based experiences with the bed rest analog support the concept that prolonged unloading, combined with reduced levels of activity, results in decreased aerobic capacity, but the development of successful exercise countermeasures is possible. Mission success during longer microgravity exposures, prolonged lunar habitation, and Mars exploration missions may be directly impacted by decreased aerobic capacity, manifested as decreased tolerance to extended work activities and the inability to respond with sufficient reserves to the high energy demands of emergency or off-nominal tasks. Specifically during lunar and Mars exploration, crews may be tasked to perform prolonged daily extravehicular activity (EVA), and in order to successfully complete these tasks, countermeasures to protect aerobic capacity will be necessary.

III. Introduction

A reduction in maximal aerobic capacity will cause a diminished capacity to perform strenuous physical tasks. With regard to space flight applications, VO_2max impacts the ability to perform an egress task while wearing the required space suit during launch and landing (14); therefore, a decreased maximal aerobic capacity may represent a safety concern in the event of an emergency, especially immediately after landing. During lunar EVAs conducted during the Apollo era, there are several reports of EVA intensity becoming high, usually manifested by heart rates reaching 150-160 beats•min^{-1} (123).

These heart rates are equivalent to approximately 78–85% of maximum heart rate. It is not certain that maximal aerobic capacity was reduced during the Apollo flights; nevertheless, it appears that lunar EVAs may have at times required high work outputs which taxed the aerobic exercise capacities of the crews.

The gold standard measure of aerobic capacity is maximum oxygen uptake (VO_2max), which is directly related to the physical working capacity of an individual (5;7). VO_2max is the maximal level of oxygen utilization that can be attained during exercise requiring a large muscle mass (102). Delivery of oxygen to the active muscles involves cardiac output (Q_c) and extraction of oxygen by the muscles measured as arterial-venous (a-v) oxygen difference. The relationship between VO_2, Q_c and a-v O_2 difference is quantified by the Fick equation (127):

$$VO_2 = Q_c \times (a\text{-}v)O_2 \text{ difference}$$

Expressed for VO_2max, the equation becomes:

$$VO_2max = Q_cmax \times max(a\text{-}v)O_2 \text{ difference}$$

Q_c is the product of heart rate (HR) and stroke volume (SV, the volume of blood ejected from the left ventricle per beat). Thus, the Fick equation can be written as:

$$VO_2 = HR \times SV \times (a\text{-}v)O_2 \text{ difference}$$

Any factor which influences maximum HR, SV or $(a\text{-}v)O_2$ difference may influence VO_2max, particularly if the change cannot be compensated for by one of the other contributing factors. For example, if SV has declined, HR might increase to compensate. However, the range of compensation may be limited; for example, HR can only increase a finite amount (that is, to an individual's HRmax).

Exposure to microgravity causes rapid changes in submaximal exercise responses and a decline in peak aerobic exercise capacity (VO_2pk) (26;58). Crewmembers who participate in short (99) (108)and long-duration space flight (105) can maintain or even improve in-flight exercise response by performing in-flight exercise countermeasures, but postflight performance under the influence of gravity or orthostatic stress is not well protected. Levine et al. (99) found that Space Shuttle crewmembers participating in flights of 9 and 14 days experienced no significant decrease in aerobic capacity during their mission, but VO_2pk was reduced by 22% immediately post flight. A study of this type has not been repeated for long-duration space flight. Results from long-duration in-flight *submaximal* exercise tests show that aerobic capacity is near preflight levels at the end of the mission (86); however, aerobic capacity as estimated by the HR response to submaximal exercise is reduced by 19% five days after landing (107). Current operational limitations prohibit VO_2max testing on landing day; thus the extent of the decrement on the most provocative mission day is unknown and is not likely to be determined in the near future.

Maintenance of upright exercise capacity after space flight – whether in full or partial gravity – is important operationally to the success of a mission and perhaps to crew

survival (92;164). For example, crewmembers may be required to perform an emergency egress from the Space Shuttle. Emergency egress represents a significant metabolic (>2.5 $L \cdot min^{-1}$) and cardiovascular (>160 $beats \cdot min^{-1}$) stress in normal ambulatory subjects (14) and would be a much greater challenge after long-duration ISS missions that typically last 6 months or more. Mission requirements during lunar and Mars exploration missions have not been well defined or characterized, but we expect that the deconditioning effects of partial- and micro-gravity exposure will impact task performance.

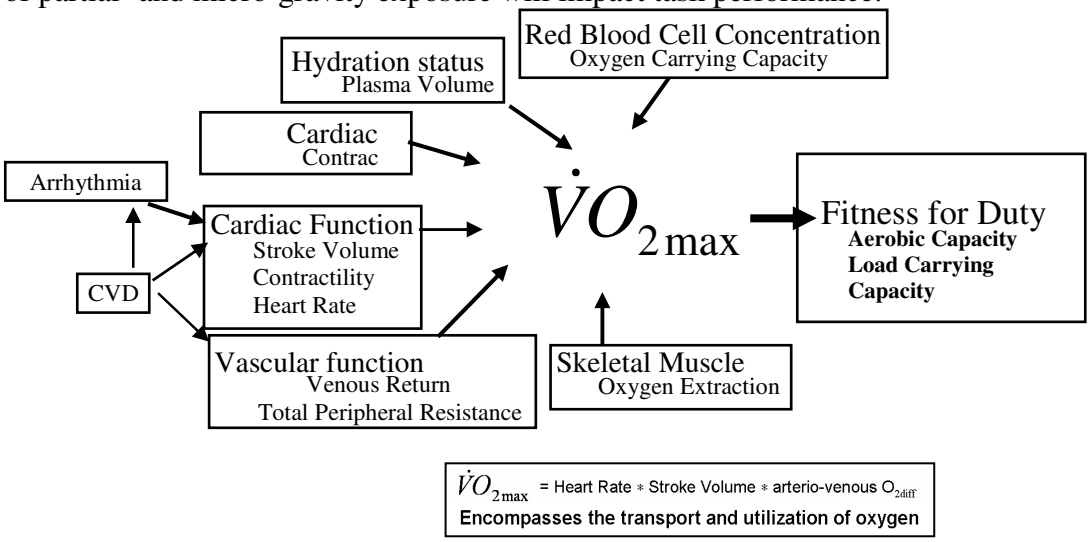

Figure 1. Diagram showing the major physiological contributors to VO_2max.

Many physiological factors influence aerobic capacity (Figure 1). The most rapidly occurring adaptation to space flight and bed rest, which appears to have a strong influence upon aerobic capacity, is plasma volume. In a review of previous investigations, Convertino (29) reported that 70% of the variability in VO_2max following bed rest deconditioning can be explained by a decreased plasma volume. Similarly, Stegemann et al. (151) reported that decreased blood volumes were related to a decreased aerobic capacity after space flight. Reduced circulating plasma volume may negatively affect exercise SV, the delivery of oxygen and nutrients to working muscle, and the removal of metabolic waste products. A reduced plasma volume is even more problematic during upright (rather than supine) exercise post-bed rest because of a possible increased pooling of blood in the lower body with gravitational stress, thus further compromising exercise cardiovascular response.

With exposures of at least 6 weeks to simulated microgravity (bed rest), structural changes in the myocardium (120) and the vasculature (172) may increasingly impair the delivery of oxygen to working muscles. Additionally, negative metabolic adaptations to simulated microgravity, such as reduced citrate synthase activity, become apparent after 4 weeks of unloading (10;72). Citrate synthase is the rate limiting enzyme in the first step of the Krebs cycle; therefore, it plays a critical role in aerobic metabolism at the cellular level. Longer durations of space flight are associated with decreased muscle mass, strength, and endurance which would be expected to impair aerobic exercise performance and decrease the efficacy of the muscle pump to protect venous return (150).

IV. Evidence

A. Spaceflight

Most of the observations regarding aerobic capacity during and after space flight reviewed in this section are derived from experiences in the U.S. space program. Most space flight studies have used the HR response to submaximal exercise loads to make assumptions about changes in maximal aerobic capacity. This practice is based upon the general observation in ground-based studies that subjects will have a higher HR at a given absolute exercise intensity when they are not well-conditioned compared to the HR that would be observed following exercise training. However, as discussed below, this method of determining changes in aerobic fitness has limitations that may lead to erroneous conclusions regarding changes in VO_2max. Unfortunately, there have been few studies in either the U.S. or Russian programs that have actually measured maximum oxygen uptake (VO_2max) during or following space flight, and these studies were conducted on short-duration (less than 14 days) space flight participants.

1. Project Mercury

The success of the sub-orbital flight of Alan B. Shepard in the Mercury space capsule "Freedom 7" on May 5, 1961, marked the beginning of manned exploration of space by the U.S. Project Mercury was conducted using small vehicles capable of holding only one occupant. These early flights were conducted to orbit a manned spacecraft around the earth, to investigate man's ability to function in space, and to demonstrate the successful recovery of both man and spacecraft safely. During the six flights of the Mercury program, two suborbital and four orbital, no studies of aerobic capacity were conducted. During the orbital flights, however, exercise tests were conducted in the space craft. Crewmembers performed a 30-second exercise session using a bungee cord with a 16-pound pull through a distance of 6 inches (169). The crewmembers' HRs were increased during exercise and rapidly recovered afterwards. These were the first demonstrations that the cardiovascular system is reactive to exercise during space flight.

Although exercise intolerance was not observed, in-flight exercise training was recommended for crewmember protection during future space flight missions. Specifically, the following quote was included in the post-mission report of the third U.S. manned orbital flight (9):

> "An orthostatic rise in heart rate, fall in systolic blood pressure, and maintenance of the diastolic pressure was noted during the 24 hours immediately after landing. Such a hemodynamic phenomenon may have more serious implications for a longer mission. A prescribed in-flight exercise program may be necessary to preclude symptoms in case of the need for an emergency egress soon after landing."

This statement indicates that exercise was being considered by NASA as a possible countermeasure for space flight exposure as early as 1962.

2. Project Gemini

The Gemini project was conducted from 1964-1966 using two-man space capsules launched to orbit atop modified U.S. Air Force Titan-II intercontinental ballistic missiles.

These flights were conducted to gain experience necessary to conduct future missions to the moon. Therefore, the objectives of these flights were to subject man and equipment to the space flight environment for periods lasting up to 2 weeks, to practice docking and rendezvous with orbiting target vehicles, and to refine the landing methodology. There were 12 Gemini flights: 2 unmanned and 10 flights with 2-person crews.

During three of the manned flights (Gemini IV-4 days, Gemini V-7 days, and Gemini VII-14 days), exercise testing was conducted as part of an experiment designated as M003 – Inflight Exercise and Work Tolerance (12). These tests consisted of crewmembers performing 30 second exercise sessions with a bungee pull device (Figure 2). The target rate of pulling was one pull per second and the device delivered a force of 70 lbs (31.8 kg) at full extension. Heart rate and blood pressure were measured during these tests, which were conducted several times during each of the missions.

Figure 2. Gemini in-flight exerciser from Dietlein and Rapp, 1966 (45).

The HR response of the crewmembers to the brief exercise session remained relatively constant within an individual throughout the flights [Figure 3;(45)]. The investigators suggested that these results indicated there were no decrements in the physical condition of the crews during flights of up to 14 days. The workloads imposed by this test were relatively mild and the testing time duration was brief, therefore, it is likely this test was not a specific or sensitive measure of aerobic capacity.

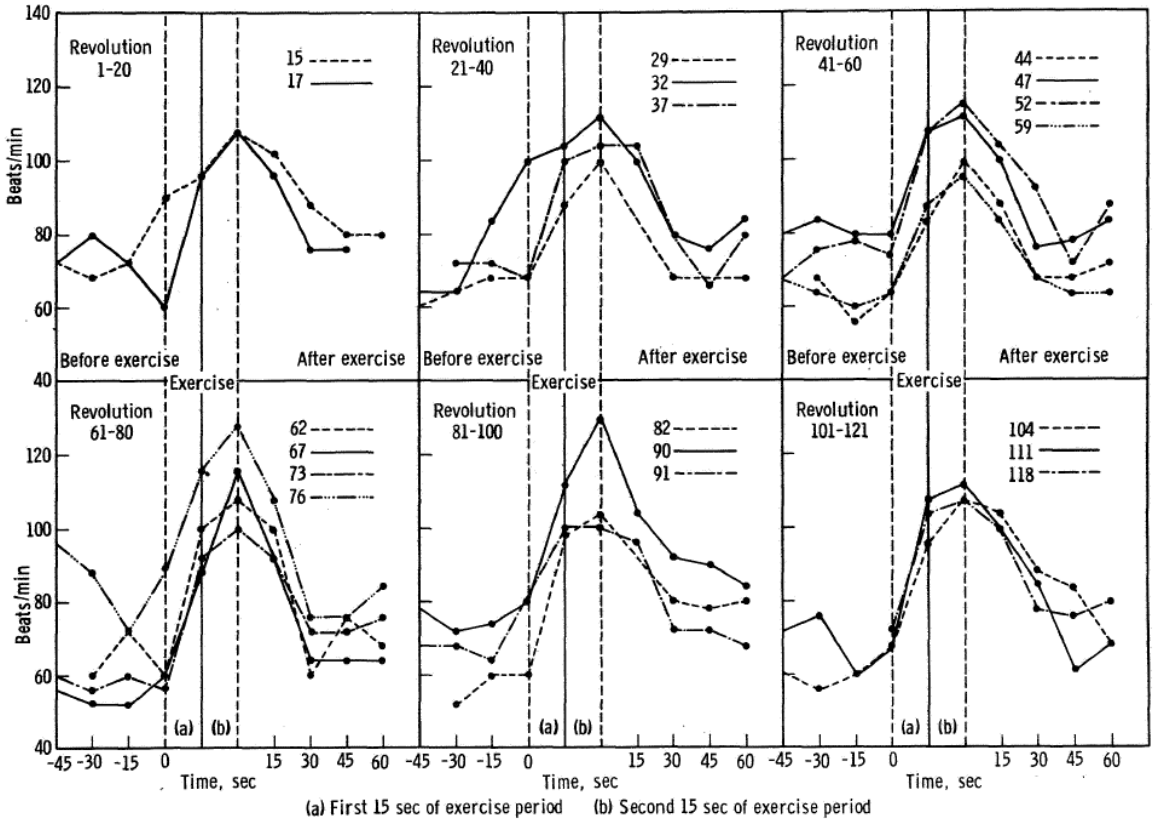

Figure 3. Example of Gemini inflight exerciser data from a single crewmember (from Barry and Catterson, 1967 (9)).

Additionally, the first preflight and postflight graded exercise tests were performed by six crewmembers from four of the Gemini flights to determine the effects of microgravity on postflight performance (12;45). The test protocol was conducted on an electronic cycle ergometer on which the crewmember pedaled at 60-70 rpm. The work rate was set initially at 50 Watts for 3 minutes and increased by 15 Watts each minute until the crewmember's HR reached 180 beats·min^{-1}. The data from these tests were never published in a comprehensive fashion, but in the NASA Gemini Summary Conference Report (12) it was reported that all but one of the crewmembers tested experienced a decrease in exercise capacity. Decline in exercise capacity was demonstrated by an increase in the HR response to exercise and a reduction in oxygen consumption at exercise termination. For example, the oxygen consumption at test termination was 19 and 26% lower after flight in the 2 crewmembers of Gemini VII (45). Figure 4 is an illustration of the graded exercise test results of a Gemini IX crewmember (12). Although these were not true measurements of VO_2max, the investigators suggested that these data provide strong evidence that aerobic capacity was compromised following the Gemini flights. The pre- to postflight decline in oxygen consumption at test termination was suggested to have been related to decreased total blood volume (reduced in 5 of 6 crewmembers examined), plasma volume (decreased in 4 of 6) and red cell mass (decreased in all 6 crewmembers). The factors that were speculated to cause these hematological changes were hyperoxia (the Gemini space craft environment was 100%

oxygen at 5 psia, or 259 mmHg), physical confinement of the crew, dietary factors, and weightlessness.

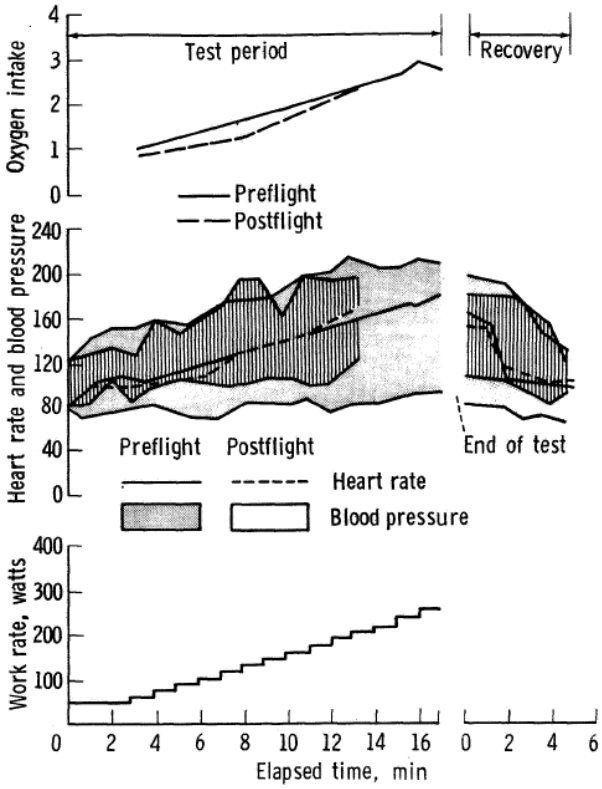

Figure 4. Gemini IX pre- and postflight exercise test results.(12)

3. Apollo Program

The Apollo program is best remembered for the flight of Apollo 11, which was the first manned exploration of the moon. The Apollo program consisted of 11 flights conducted between 1968 and 1972. Of these flights, six delivered astronauts to the moon's surface. The Apollo crews consisted of 3 men per flight and the flight durations ranged from 5.9 to 12.7 days.

The crews of Apollo 7-11 and 14-17 (n=27) participated in submaximal exercise testing to quantify pre- to post flight changes in the physiological response to exercise (11;128;130;132). An electronically-braked cycle ergometer was used for exercise testing with which work rate was controlled using a HR feed-back loop, and VO_2 (L/min) was measured during these exercise tests.. The test protocol consisted of 3 exercise work rates which produced HRs of 120, 140 and 160 beats·min^{-1}. The Apollo 9 and 10 crews also performed an additional stage which elicited a HR of 180 beats·min^{-1}. The oxygen consumption (that is, exercise work rate) at all exercise stages was significantly less on landing day (R+0), but was near pre-flight levels 24-26 hours following landing (R+1; Figure 5). Exercise Qc measurements also were obtained from the crews of Apollo 15-17 and indicated that a reduction in SV (from 145 ± 34 ml·beat^{-1} to 92 ± 34 ml·beat^{-1}) led to the increased HR response to exercise on R+0. Although the HR response to exercise increased, the increase was not enough to compensate for the decline in SV as Qc was

37% lower on R+0 than it was before flight; however, it was only 7% reduced (not statistically different) from preflight on R+1. The mean pre- to postflight change in plasma volume of the Apollo astronauts was -4.4 ± 1.7% on R+0 and +4.8 ± 2.2% on R+1 (87). The rapid normalization of the crewmembers' responses to exercise suggests that changes in plasma volume played a role in the postflight decline in VO_2 at the terminating workload.

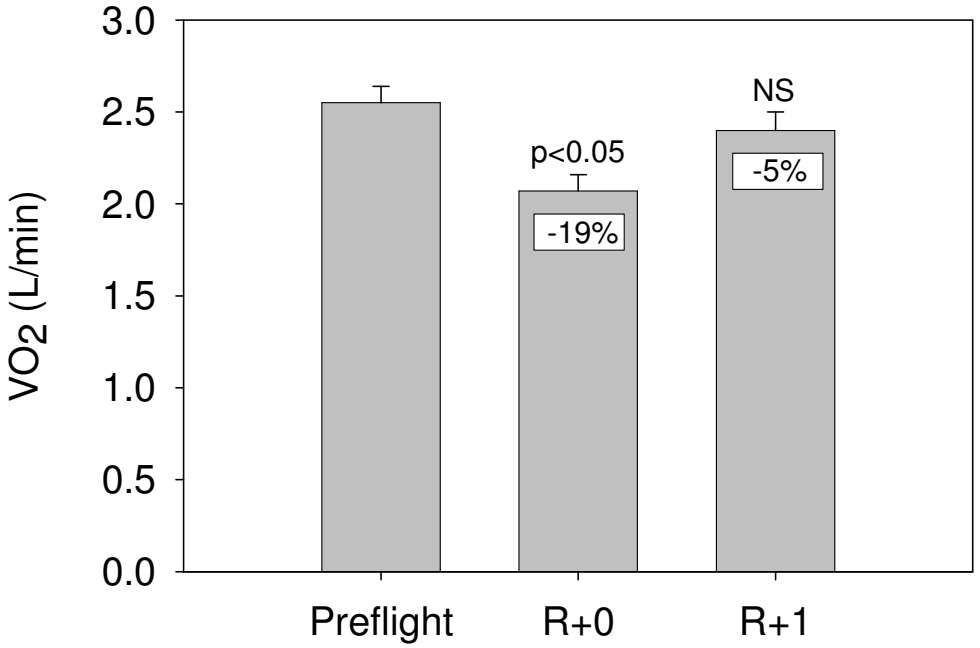

Figure 5. VO_2 changes at exercise stage eliciting a HR of 160 beats/min (Apollo crews n=27).

4. Skylab Program

The Skylab program was the first U.S. space station and the first experience with longer duration space flight. The station was launched in May 1973 atop a Saturn V vehicle, the last launch of the rocket that first took man to the moon. Three crews traveled to Skylab using Apollo-era command modules launched on Saturn 1B vehicles. The missions were 28 days in duration (Skylab 2), 59 (Skylab 3) and 84 (Skylab 4). Medical activities accounted for approximately 7% of the mission time during flight.

During the Skylab missions, routine submaximal graded exercise testing was performed on a cycle ergometer, and expired metabolic gasses were analyzed to determine VO_2 [(104;105;129)] (Figure 6). The submaximal exercise consisted of 5-minute stages of rest followed by exercise at work rates eliciting 25%, 50%, 75% and 25% of preflight VO_2max. Preflight VO_2peak was established during previous graded exercise tests to volitional fatigue conducted at L-360 and repeated at L-180. The submaximal exercise test was repeated approximately every 6 days during each flight, starting with flight day 6. There was no trend in the in-flight submaximal HR data, which was taken as an indicator of no change in the aerobic fitness of the crews; the in-flight HR at the 75% work rate was not significantly changed from preflight values in 8 of the 9 crewmembers. Cardiac output was not measured during flight, but it was measured

during the exercise tests performed before and several times following flight (19). The mean Q_c of all crewmembers at the 75% work stage was decreased by approximately 30% and SV was decreased by 50% on R+0. Within 10 days after landing, Qc and SV were within 10% of preflight values, but complete recovery was not noted until 31 days following flight. The HR response to exercise was markedly elevated immediately following flight and gradually returned to preflight levels by R+24 days. Plasma volume declined by 12.5% on R+0 and returned to preflight values by R+14 days (76). These changes did not appear to be related to mission duration. Although VO_2max was not measured in these subjects, the postflight exercise responses were assumed to be consistent with a decrease in aerobic capacity during the early recovery period and a gradual return to preflight levels over the month following flight.

An attempt was made to collect VO_2max data during instrumented personal exercise sessions to near-maximum exercise levels on four crewmembers of the Skylab 3 and 4 missions (137). However, a number of problems prevented accurate measurement of VO_2max. The Skylab cycle ergometer was limited to a work rate of 286 Watts, and 3 of the 4 crewmembers were able to exceed this work rate during preflight testing. Therefore, these 3 crewmembers performed prolonged work at 286 Watts during flight to elicit a "maximum work load." The limiting factor for these sessions was leg fatigue, rather than a true cardiovascular maximum effort. The device that measured expired ventilation (a component of the measurement of VO_2) could only accurately measure values up to 150 $L \cdot min^{-1}$, and this level was exceeded in several tests, possibly because of the low cabin pressure of Skylab (259 mmHg). The investigators concluded that the VO_2max of the crewmembers was likely maintained and perhaps even increased during flight, although the measurement hardware limitations greatly cloud the interpretation of the data.

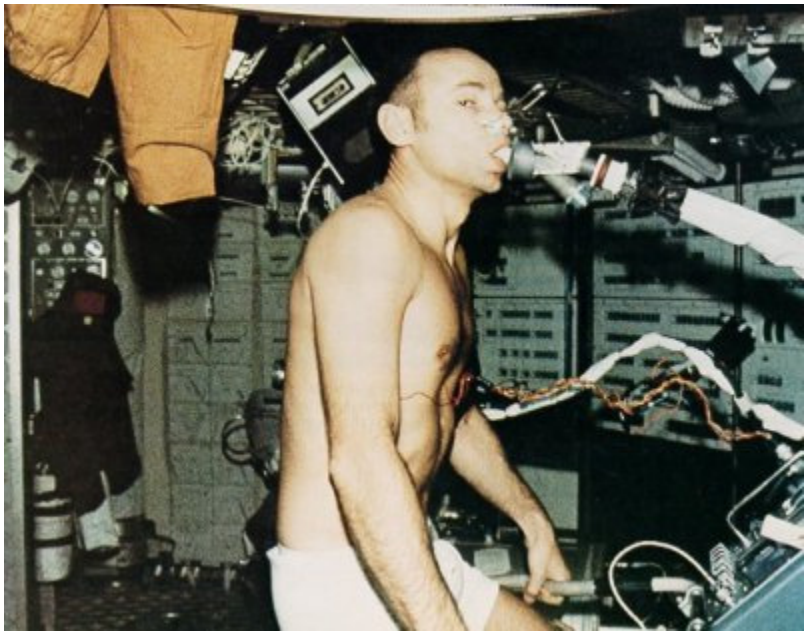

Figure 6. Skylab crewmember performing cycle exercise test with VO_2 measurements.

5. Space Shuttle Program

The first launch of the Space Shuttle program was in April 1981. The Space Shuttle is unique in that it is the first winged space vehicle that is designed to be launched from the ground and return to Earth to be reused. There have been five Shuttle orbiters, two of which were destroyed – one during launch (*Challenger*, January 1986) and the other during deorbit operations (*Columbia*, January 2003). The payload capacity of the Space Shuttle is considerable (22,700 Kg mass and 1,106 m^3 volume). Five to seven astronauts typically fly on a Space Shuttle mission. The intended use of the Space Shuttle from its inception was to support the future space station, which at the time of this writing is the primary use of the vehicle. However, for the majority of the Space Shuttle program the vehicle has been used to transport large payloads into orbit (such as the Hubble space telescope) and to conduct other low-Earth operations. The Space Shuttle cargo bay was also used to carry a laboratory, such as the Spacelab and SPACEHAB™ modules, in which human life sciences experiments have been conducted.

The studies that have actually measured VO_2max prior to, during, and immediately following space flight have been conducted during the Space Shuttle era. Of these, only one study measured VO_2max during space flight. Levine and co-workers (99) reported the results of peak cycle ergometer tests on six astronauts during the Spacelab Life Sciences (SLS)-1 (9 day) and SLS-2 (14 day) missions. VO_2max measured between flight day 5 and 8 was not different than preflight VO_2max. Interestingly, submaximal Qc, measured on the same flights and same days as the astronauts reported on in the Levine study (99), was lower during space flight (144). Shykoff, et al. (144) speculated that either the Qc needed to support moderate to heavy exercise is less in microgravity than on the ground or that a reduction in circulating blood volume caused by the storage of blood in the pulmonary circulation limited the increase in Qc by reducing the SV. Reduced submaximal Qc during space flight is difficult to reconcile with the observation that VO_2max did not change during flight in these subjects (99). However, Alfrey and co-workers reported that plasma volume was reduced by 17% on flight day (FD) 1 and 12% on FDs 8-12 during these space flights (2). Subjects experienced a mean reduction in VO_2max and Qc of 22% and 24%, respectively, on landing day while there was no change observed in maximum HR. Levine and colleagues (99) concluded that the reduction in maximum Qc, and thereby VO_2max, was due entirely to changes in SV. The reduction in SV was likely due to impaired venous return caused by a decrease in plasma volume, which remained depressed on the first recovery day (2). VO_2max recovered by approximately 50% on R+1-2 and had fully recovered to preflight levels by R+6-9 (Figure 7). Plasma volume had recovered to preflight values on R+6 (2).

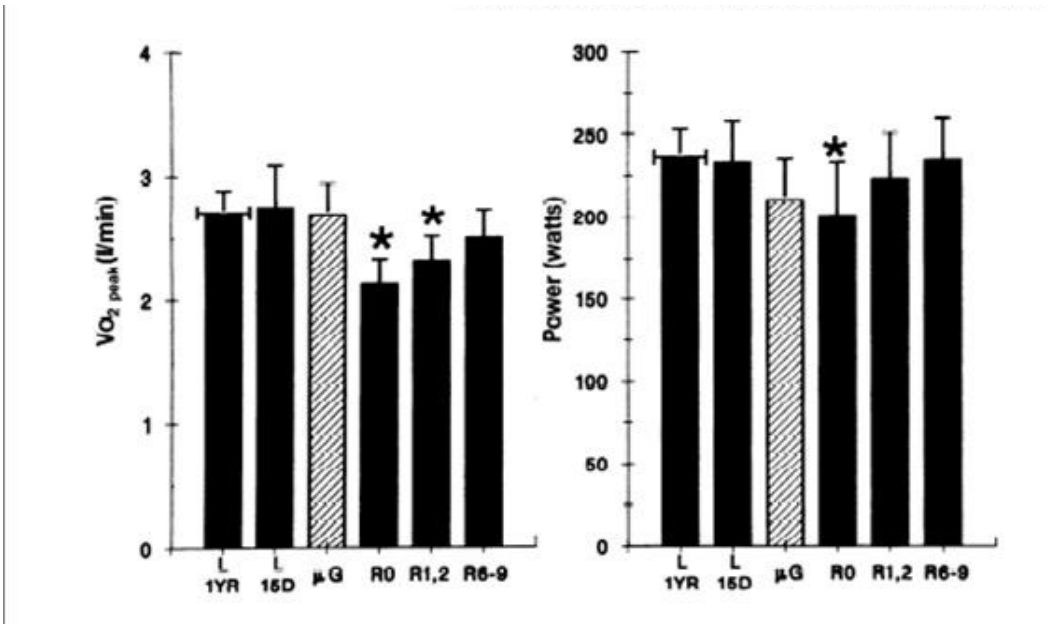

Figure 7. VO_2 max was not changed during the SLS-1 and SLS-2 flights; however it is decreased in the first 2 days following flight (from Levine, et al, 1996 (99)).

Moore and co-workers (108) reported exercise results that are consistent with the SLS-1 and SLS-2 findings. The primary intent of this study was to determine if maximal exercise performed on the last day of flight would preserve postflight orthostatic function and aerobic capacity, as suggested by a previous bed rest study by Convertino and coworkers (25). Astronauts (n=8) participating in flights ranging from 8-14 days in duration performed a peak cycle ergometer test before flight and again on the last full flight day. Although VO_2 was not measured during flight, the HR response to exercise during flight did not differ from that measured preflight, and the peak work rate performed during these tests was not different from that performed before flight. Both of these observations suggest that VO_2max was unchanged during flight. However, when VO_2 was measured during exercise testing on landing day, the crewmembers experienced a decline in VO_2max ranging from 11-28% (mean decline 18%). Three days following flight, VO_2max still was reduced an average of 11%, but VO_2max had returned to baseline values by R+14. Similar to the findings of Levine and colleagues (99), maximum HR did not change following flight; thus it is likely that reductions in Qc and SV played a role in the decrease in VO_2max on R+0 and R+3.

In contrast to the studies reported by Levine (99) and Moore (108), Trappe et al. (161) reported results consistent with aerobic deconditioning during a Space Shuttle flight. Exercise tests were limited to 85% of preflight VO_2max during flight and up to 4 days following flight. The 4 subjects on the 16-day STS-78 flight demonstrated a mean increase of 7% in exercise HR at the 85% workload on FD 8 and 9% on FD 13, which was interpreted as a sign of aerobic deconditioning. The difference between these results and those reported previously (99;108) are not readily explainable, but may have been related to differences in the preflight fitness levels of the crewmembers participating in the studies [Trappe et al. (161): 3.59 $l \cdot min^{-1}$, Moore et al. (108): 3.29 $l \cdot min^{-1}$, Levine et al. (99): 2.76 $l \cdot min^{-1}$], exercise countermeasures and other physical testing performed during the flights, or individual differences in the response to space flight (degree of space

motion sickness, medications used, etc.). It is also possible that, similar to the data observed by Shykoff et al. (144), submaximal Qc (caused primarily by a lower SV) was decreased in these subjects, and submaximal HRs were increased as a partially compensatory response. Cardiac output and SV were not measured in the study reported by Trappe et al. (161). On R+4 and R+8, VO_2max was reduced by 10.3% and 5.0%, respectively. This finding follows the general trend of recovery in VO_2max observed by both Levine et al. (99) and Moore et al. (108) .

Investigations related to exercise capacity and the preservation of the cardiovascular responses to exercise were conducted by NASA during the Extended Duration Orbiter Medical Project (EDOMP) from 1989 to 1995. These studies were: 1) designed to be relevant to space flight operations, 2) required to be related to performance of the crewmembers during entry, landing, or egress from the Space Shuttle, and 3) conducted as NASA Detailed Supplemental Objectives (DSOs). DSO studies are limited in the amount of hardware stowage that can be used to support the studies during flight; therefore, the majority of these involved pre- vs. postflight comparisons. In addition, fairly early in EDOMP, NASA's Committee for the Protection of Human Subjects limited the intensity of exercise investigations during and immediately following space flight to levels of no greater than 85% of preflight VO_2max. The authors of this report are not aware of any cardiovascular anomaly that occurred either during or following flight that precipitated this exercise limitation. In any event, this restriction is the reason for the limitation of exercise intensity of the subjects of Trappe and colleagues (161) and for subsequent investigations. The study reported by Moore (108) was the final investigation which utilized maximum exercise testing during or immediately following space shuttle flight.

Despite the above listed limitations, studies conducted during the EDOMP era produced findings related to the space flight-induced decrease in aerobic capacity. One study examined the effects of continuous vs. low-level interval exercise on postflight aerobic capacity (145). During flight the subjects (n=17) performed one of two exercise prescriptions on a small passive treadmill or served as controls (Figure 8). HR was used by the exercising crewmembers to regulate exercise intensity. Treadmill testing to measure VO_2max was performed before and 2 days following flight. The subjects who exercised during flight demonstrated no statistically significant decrease in VO_2max, while the control subjects experienced a 9.5% loss. Although this study did not measure VO_2max immediately following flight, it did demonstrate that VO_2max response 2 days following flight could be altered by in-flight training.

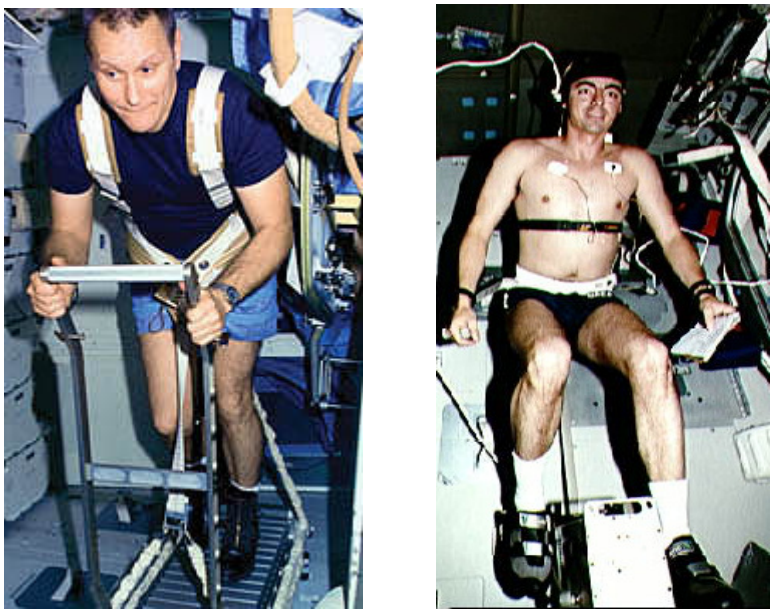

Figure 8. Astronauts exercising on passive space shuttle treadmill and the Shuttle cycle ergometer.

Another study conducted during EDOMP was designed to monitor aerobic exercise performed during flight and the influence of this exercise on the HR and VO_2 responses to exercise testing following flight (59). Astronauts (n=35) performed incremental (50 Watts for 3 minutes, followed by 50 Watt increases every 3 minutes) upright cycle ergometer exercise tests with VO_2 and HR measurements prior to flight (L-10) and on landing day (R+0). These tests were terminated at the work stage that elicited 85% of each participant's age-predicted maximum HR; VO_2max was not measured. Exercise countermeasures for use during flight were not prescribed, but each astronaut wore a HR monitor that recorded both the HR and duration of their exercise sessions. One mission included both a treadmill and a cycle ergometer as exercise modalities, but the treadmill was used for only two exercise sessions by one crewmember (Figure 8). The remaining inflight exercise conducted during this study was performed on the Space Shuttle cycle ergometer. The major finding of the study was that astronauts who performed regular aerobic exercise during flight demonstrated a smaller decline in VO_2 at the termination workload (thus their exercise HR was less elevated) than did astronauts who exercised less frequently or at a lower intensity (Figure 9). Regular aerobic exercise was defined as three or more sessions per week, each session lasting at least 20 minutes, and at an intensity that elicited a HR of > 70% of their age-predicted maximum HR. Q_c was not measured in these subjects, but the relative tachycardia experienced by the crewmembers on landing day is consistent with a compensation for lowered SV. Though speculative, it is possible that plasma volume was better maintained in the "regular exercise" subjects. Lee and co-workers who reported on the R+0 stand test findings of these subjects (91), observed a greater HR response and reduced pulse pressure (often used as an index of SV) during standing in the "minimal" exercise subjects. Thus, it appears that, at least for Shuttle duration flights, a decline in VO_2max immediately following flight may be partially attenuated by exercise conducted during flight.

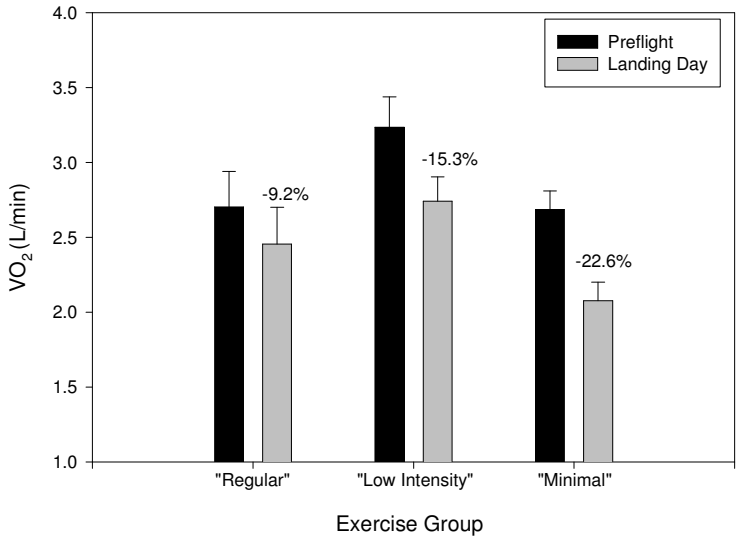

Figure 9. Oxygen consumption achieved at 85% age-predicted maximum HR pre- and post-flight in crewmembers (n=35) who participated in different amounts of in-flight exercise.
"Regular" (n=11) - Exercised > 3x/week, HR > 70% age-predicted, > 20 min/session
"Low Intensity" (n= 10) - Exercised > 3x/week, HR < 70% age-predicted, > 20 min/session
"Minimal" (n=14) - Exercised < 3x/week, HR and min/session variable. Redrawn from Greenisen, et al (59).

6. International Space Station (ISS)

The ISS is an orbiting research facility that, at the time of this writing, is still being assembled in low-Earth orbit. ISS assembly in space was initiated in 1998, and a manned presence on board ISS has continued since November 2000. The crews of the ISS have been comprised of U.S., Russian and European Space Agency (ESA) astronauts, and the crew size for ISS Expeditions has varied between two and three long-duration occupants. Supplies and crewmembers are ferried to and from ISS on both the Space Shuttle and Russian vehicles. Sixteen long-duration expeditions have traveled to the ISS, with crewmembers visiting the station on missions ranging from 117 to 198 days.

ISS crewmembers perform treadmill, cycle ergometer, and resistive exercise during their missions to counter the effects of long-duration space flight exposure (Figure 10). Equipment availability has varied throughout the history of the ISS, and a standardized exercise prescription has not been utilized. The treadmill (TVIS – Treadmill with Vibration Isolation System) is motorized; however, there have been times when the motor was not functioning and the crewmembers had to use it in a passive, or non-motorized, mode. At times the crewmembers have chosen to use the TVIS in the passive mode and/or speed restrictions have been placed upon the device to limit the consumption of station power resources by the device. The TVIS is vibration isolated from the ISS using a set of active counter masses and a large gyroscopic device that are located under the device. The Cycle Ergometer with Vibration Isolation System (CEVIS) is also vibration isolated from the ISS using a counter mass system and a passive system of wire isolators located on the corners of the frame. The CEVIS is capable of exercise loads from 25-350 Watts (controllable to 1 Watt increments) and also allows stable work rates to be applied between pedaling rates of 50-120 rpm. The interim Resistive Exercise Device (iRED) used on board ISS consists of two canisters, each containing a series of elastomer-spoked wheels (otherwise known as “FlexPacks”). A non-elastic cable attached to the stack of FlexPacks is routed through a spiral pulley and extends from the

base of each canister to attach to a subject loading device (either a body-worn harness or an exercise bar). Extending the cables during the concentric portion of an exercise turns a spline and rotates the inner-ring of the FlexPacks; this stretches the elastomer spokes and generates a resistive force. An eccentric load is generated as the cable subsequently recoils. However, the eccentric-to-concentric force ratio is only ~60-80%. Rotating a handle attached to the top of each canister alters the initial stretch of the FlexPacks and allows the user to adjust the magnitude of the resistive force. The iRED is limited to 300 lb. of total force (96). During early ISS missions its function was unreliable and the number of sets and repetitions that a crewmember was allowed to perform was limited to increase the life of the FlexPack resistance mechanism. ISS also has a second cycle ergometer device, know as the veloergometer (Figure 11). The veloergometer is a Russian-designed cycle ergometer capable of controlled loads ranging from 100 to 250 Watts (in 25 Watt increments); it is not vibration isolated from the ISS. Typically, crewmembers perform treadmill exercise 4-6 sessions per week for 30-45 minutes, cycle ergometer exercise 2-3 times per week for 30-45 minutes, and resistive exercise training up to 6 sessions per week, performing primarily exercises to maintain strength in the lower body and trunk. Two and one-half hours per day is scheduled for exercise sessions, including time to change into exercise clothing and clean up following activity so the effective daily exercise time is about 1 hour and 15 minutes.

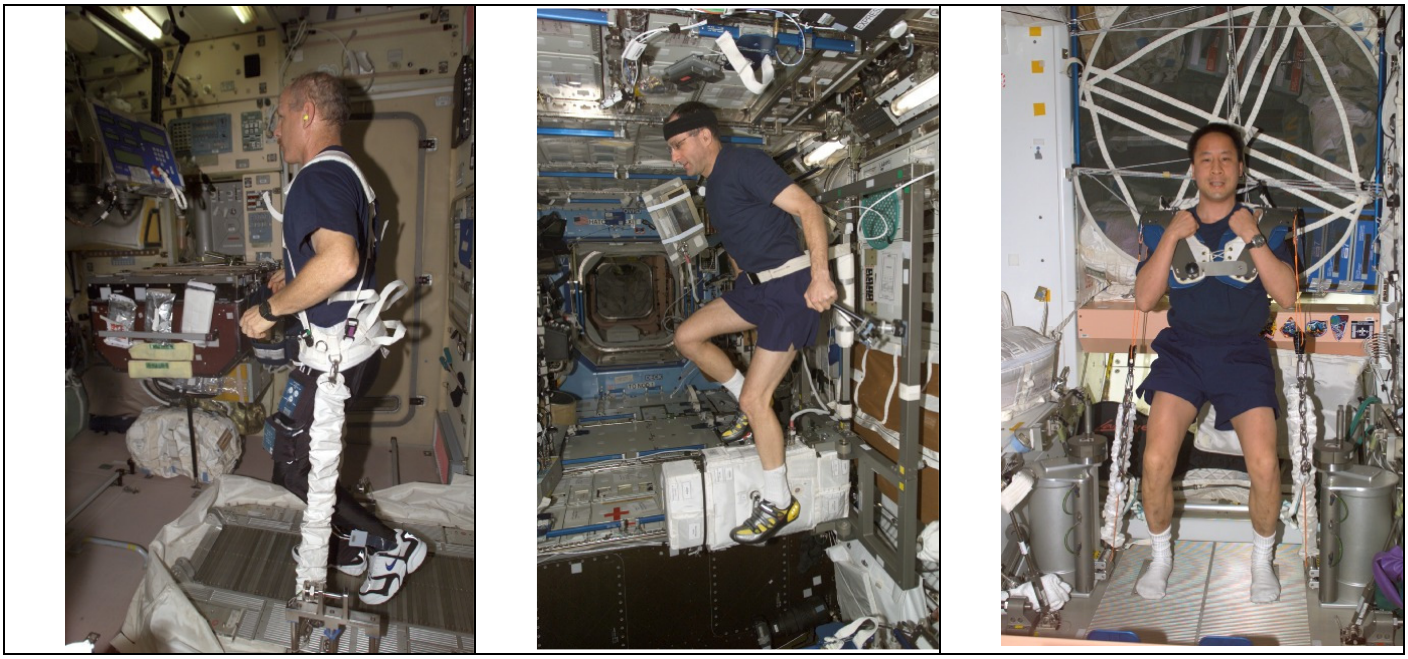

Figure 10. International Space Station crewmembers exercising on the treadmill with vibration isolation system (left), the cycle ergometer (center), and the interim resistive exercise device (right).

Figure 11. The Russian veloergometer device.

Cycle ergometer testing has been performed on U.S. and ESA crewmembers before and after all but the first ISS mission; in-flight testing has been performed using the CEVIS. Testing to establish preflight VO_2max and HRmax is performed by each crewmember approximately 9 months (L-270; 270 days prior to launch) before flight. Subsequent testing, using a submaximal test protocol similar to that of the Skylab crews, is scheduled to be performed on L-30, FD 15, every 30 FDs following the initial in-flight test, and on recovery days R+5 and R+30. In-flight measurements of VO_2 were planned for all testing sessions, but technical and budgetary issues prevented a metabolic gas analysis system from being flown to the ISS until very recently. Pre- and postflight tests have been performed with VO_2 measurements, but in-flight tests have been performed using only HR monitoring (via ECG and a separate HR monitor). The HR data obtained during the in-flight tests and the VO_2 data obtained during the preflight tests are used (this assumes no change in the metabolic cost of cycle exercise during flight) to estimate VO_2max using a linear extrapolation method (Figure 12). This method is commonly used during field testing of subjects (5;7) and has been demonstrated to be a good indicator of the mean VO_2max of a group, but the variation from an actual measure of VO_2max in an individual can be substantial (98).

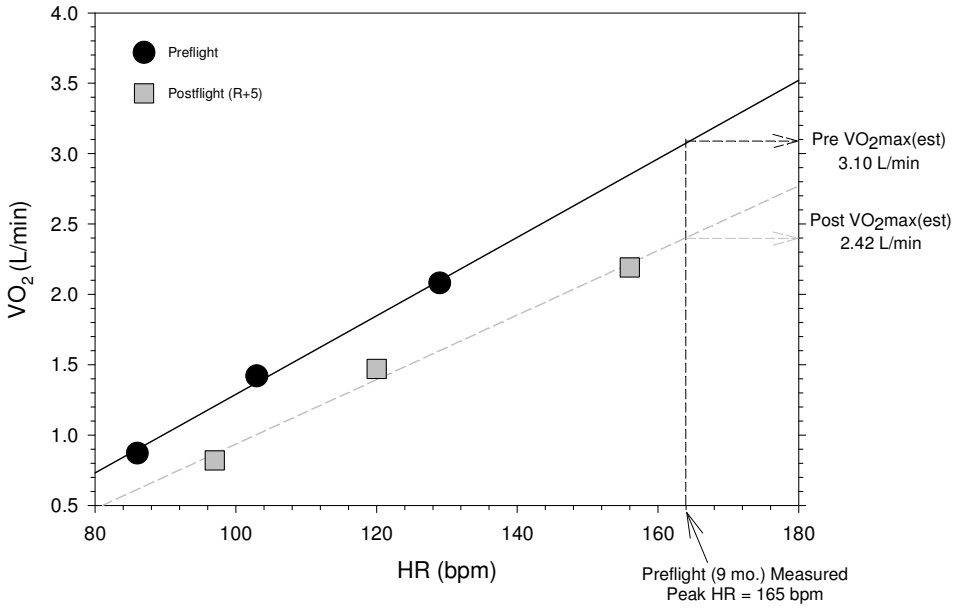

Figure 12. Linear extrapolation method of estimating VO_2max. The illustrated data is from an ISS crewmember.

The elevated HR response during the exercise tests from early in the ISS missions indicate that estimated VO_2max is reduced by an average of 19% (Figure 13). Some recovery (lowering) of the HR response to the same absolute exercise work rates occurs throughout flight, and the estimated VO_2max is typically recovered to within 10% of pre-flight later during the missions. These data differ from that reported during the Skylab era (104;105;129) when the HR response to exercise during flight did not differ from preflight values.

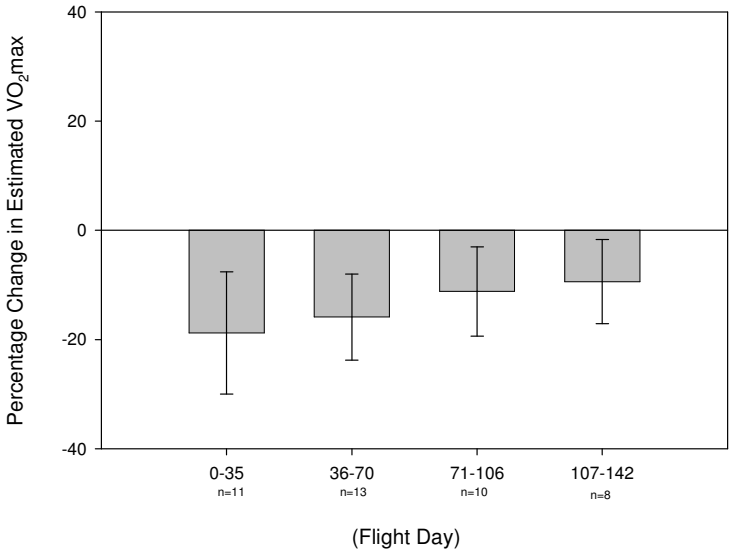

Figure 13. Percentage change in VO_2max during ISS flights, estimated from changes in the HR response during submaximal exercise tests. Data from unpublished ISS medical testing.

Following missions to the ISS, VO_{2s} measured during the submaximal exercise tests are not different than preflight, but the HR response to the same absolute exercise work rate is elevated on R+5. Plasma volume is normalized to preflight levels by R+5 (Dr. Steven Platts, personal communication); therefore, the elevation in HR may be due to a combination of lowered erythrocyte mass and muscular detraining. The ISS crewmembers' estimated VO_2max values on day R+5 decline an average of 16% from preflight values (Figure 14), which is similar to the actual VO_2max change on R+0 during Shuttle flights (99;108). This is much greater than that reported between R+1 and R+9 in Shuttle crewmembers (160), suggesting that the deconditioning experienced by ISS crewmembers is greater, or lasts longer than that experienced by Shuttle crews. The HR response to exercise is not different than pre-flight by R+30; therefore, it is assumed that VO_2max is recovered in ISS crewmembers by this time. It is unclear, however, if VO_2max had recovered to preflight values at an earlier time.

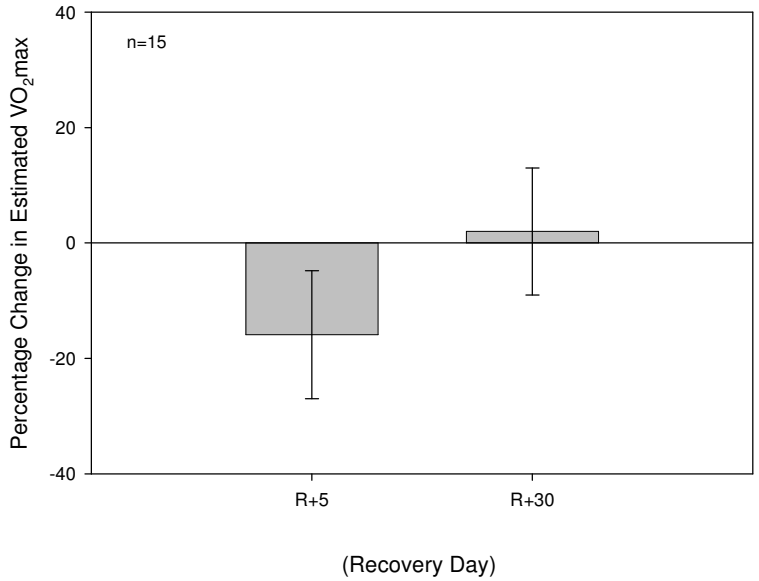

Figure 14. Percentage change in estimated VO_2max following ISS flights. Data from unpublished ISS medical testing.

The Russian cardiovascular exercise test data from four cosmonauts during ISS flight is remarkably similar to that observed in the U.S. tests reported above (122). Russian cosmonauts perform a cycle test, designated as MO-3, on the veloergometer every 30 days during flight. This test is conducted using 3 minute stages at 125, 150, and 175 Watts. The HR response to exercise of these cosmonauts was greatest during the test that was performed 1 month into flight and became progressively lower as flight duration increased. This response is consistent with an initial decline and recovery of VO_2max during flight. The authors of the Russian report referred to the initial phase of flight as a "dead period" during which the decrease in physical condition is so severe that none of their countermeasure regimes were sufficiently effective. However, the Russian crewmembers exercise little during the first couple of weeks during flight and this may contribute to the increased HR response noted early during flight.

7. Limitations in the Interpretation of Long-Duration Aerobic Exercise Data from ISS

Estimation of changes in aerobic capacity using changes in exercise HR is of questionable accuracy during and following space flight due to several factors. For example, microgravity-induced hypovolemia is expected to elevate the HR response to exercise in the very early postflight period: whether or not this elevation in HR is highly associated with postflight decrease in aerobic capacity remains undetermined. With regard to inflight measures, the current approach to estimatingVO_2max during space flight assumes that the VO_2 required to perform cycle ergometry during flight is not different than that measured during pre-flight testing. Although the Skylab submaximal exercise VO_2 data would support this assumption, preliminary data collected from ISS astronauts indicate that submaximal VO_2 measured inflight may differ from preflight values (Dr. Alan Moore and Frank McCleary, personal communication). A plausible explanation for differences between Skylab and ISS cycle VO_2 data is that the Skylab cycle was hard-mounted to the vehicle, but the ISS ergometer is mounted to a vibration isolation system that is then attached to the vehicle. The ISS CEVIS is isolated from the station structure by wire rope loop balls on all four corners of the mounting frame, and the cycle tends to sway during exercise. Although the exercising astronaut is affixed to the CEVIS via cleated cycling shoes, the transmission of muscular force to the cycle may be less efficient than experienced during the "normal" cycle ergometry performed preflight. Therefore, the metabolic cost of performing exercise during flight on the CEVIS may vary from preflight and invalidate an assumption used to estimate VO_2max from submaximal data. However, the tests performed by the Russian crewmembers on the veloergometer (a non-vibration isolated device) indicate an increased HR response to exercise which is more pronounced early during flight (122). Therefore, it is also plausible that the increases in HR observed during exercise tests on board ISS represent aerobic deconditioning. Even if the oxygen cost of exercising on the CEVIS is found to be similar to that of ergometry performed on the ground and even under the best of circumstances, estimating VO_2max from submaximal exercise responses works well for groups of people, but it may provide erroneous results for individuals (98). The routine submaximum cycle tests performed on ISS are sometimes waived or are performed on days other than the normal plan due to mission dictates, thus an accurate characterization of the changes experienced by crewmembers over the course of a mission is not always possible. Accurate information regarding aerobic change during long-duration space flight will not be available until regular actual measurements of VO_2max are performed on the ISS.

8. Effect of Reduced VO_2max on Space Flight Operations

The goal of any countermeasure to space flight exposure is to preserve the capability of the crewmembers to perform daily tasks and maintain a reserve to enable survival in emergency situations. With regard to routine tasks conducted on board the ISS, the preservation of aerobic capacity is not likely important as there are few, if any, physically strenuous routine tasks that are performed. EVAs typically elicit an average metabolic cost of ~ 200 $kcal \cdot hr^{-1}$(~0.7 Liters $O_2 \cdot min^{-1}$) and have ranged up to 500 $kcal \cdot hr^{-1}$ (~1.7 Liters $O_2 \cdot min^{-1}$) (63). The upper value represents approximately 50% of the typical astronauts aerobic capacity; however, because EVA activity is predominantly upper body

in nature, and upper body VO_2max is approximately 70% of that measured in the legs, EVAs can become aerobically challenging. The metabolic cost of performing an emergency egress task in the NASA Launch and Entry suit has been reported as ranging from 2.0-2.7 Liters $O_2 \cdot min^{-1}$, depending upon the amount of G-suit pressurization employed (14). With regard to EVA on the lunar surface during the Apollo era, several EVAs reportedly were slowed by request of the monitoring flight surgeons as heart rates during the activities reached 150-160 beats•min^{-1} (123). Until the mission scenarios are defined for future EVA work it is difficult to predict precisely what aerobic capacity will be required to successfully complete all tasks; however, it is likely that with extended stays on the moon or Mars, the importance of maintaining aerobic capacity will not diminish.

9. Flight Data Summary

As early as the Gemini Project, data exists – although limited – suggesting that during short-duration space flight the HR response to exercise, and likely VO_2max, is well-maintained but the postflight response is significantly compromised. The flight data of Levine (99) is the only conclusive evidence that VO_2max is unchanged during short-duration space flight, and the maintenance of work capacity during flight as reported by Moore (108) is strong corroborating data. However, contradictory data also exists (161) and may be partially explained by differences in the initial aerobic capacities of the crews and other factors unique to the subjects and missions.

There have been no direct measurements of VO_2max either during or immediately following long-duration space flight. Measurements of HR response to submaximal exercise during long-duration space flight have yielded conflicting results. The data from Skylab, showing no elevation in exercise HR response to exercise during flight, would seem to indicate that aerobic capacity is not altered during flights of up to 84 days (131). However, the data collected on board ISS by both the U.S. and Russian scientists and crewmembers show an elevation in the HR response to exercise that is pronounced early in flight (<45 days) and slowly returns toward preflight values (107;122). This seems to indicate that aerobic detraining occurs rapidly during flight; however, with the performance of exercise countermeasures, the degree of detraining may be attenuated and reversed. However, interpretation of the ISS in-flight findings must be viewed with caution as preliminary data also suggests that the oxygen cost of performing submaximal cycle exercise may be altered in ISS, perhaps due to factors related to the vibration isolation of the CEVIS.

Though there have only been two studies that have measured VO_2max upon landing and both of these studies were conducted following short-duration missions, the data consistently demonstrates that VO_2max is lower on landing day than it is before flight and recovers within 6-9 days following flight (99;108). Data from submaximal exercise tests conducted in the Gemini (12), Apollo (130), and Shuttle (59;160) programs all support the notion of reduced aerobic capacity immediately following flight with a rapid recovery. Data collected after long-duration space flight is confined to measurements conducted during submaximal exercise tests. Nevertheless, these data appear to be consistent with aerobic deconditioning in the first week following flight, with a return to baseline measurements within a month (107;122).

B. Ground-based Space Flight Analog (Bed Rest)

Human physiology studies during space flight are difficult to perform due to the limited number of subjects available and multiple confounding factors, including variable adherence to prescribed countermeasures, inconsistent dietary practices (146), participation in other science experiments, and interference of specific mission task requirements (161). Bed rest has become an accepted and established model to study changes in physiologic function associated with space flight, including changes in aerobic capacity (58), in a more controlled environment(119). In general, the reduction in VO_2max as a result of bed rest is considered to result from the combined effects of reduced physical activity and removal of the effects of orthostatic stress (24). In a direct comparison between responses after space flight and bed rest, Trappe et al. (161) reported that the decrease in aerobic capacity during supine cycle ergometry in 4 crewmembers 4 days after a 17-day mission (-10.4%) was comparable to that observed in 8 subjects (-6.6%) 3 days after a 6° head-down tilt bed rest of the same duration (Figure 15). No similar comparisons are yet available for long-duration missions and no bed rest studies have been conducted to mimic the countermeasure protocols in which astronauts and cosmonauts aboard ISS currently engage (67;82;83).

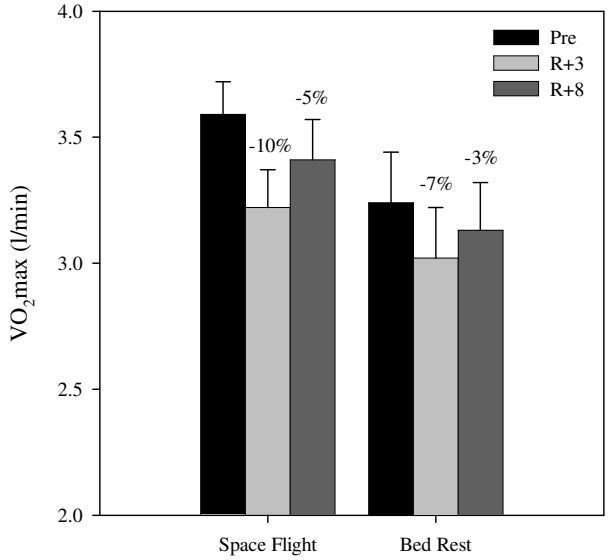

Figure 15. VO_2max before, 3 days after (R+3), and 8 days after (R+8) 17 days in space or bed rest (161).

1. Changes in VO_2pk with Bed Rest

(a) Duration

In general, there is a rapid decline in VO_2max with the first few days of bed rest and a more gradual loss thereafter (24;29). Nixon et al. (115) reported a decrease in VO_2max, estimated from upright cycle ergometer test duration, of 22% (Pre: 36.4±2.4; Post: 28.5±2.0 $ml \cdot kg^{-1} \cdot min^{-1}$) following only 24 h of 5° head-down tilt bed rest. During bed rest periods up to 30 days, the average decrease in aerobic capacity occurs at a rate of

0.8-0.9 $\%\cdot d^{-1}$ (26;29;31). However, if aerobic capacity continued to decrease linearly in this fashion, the decrease in VO_2pk would be predicted to be 42% by 60 days and 72% by 90 days of bed rest, which overestimates the reduction in VO_2pk in longer duration bed rest studies [Hagan, in review] and would reach zero (death) within 122 days (22).

Capelli et al. (22) proposed an alternative model based upon measurements during 14, 42, and 90-day bed rest studies. Subjects in their studies experienced a decrease in aerobic capacity of 14% on day 14, 16% on day 42, and 32% on day 90 of bed rest. These investigators suggested that most of the decrease in exercise capacity occurs in the first 2 weeks and that the rate of decline is much smaller thereafter. The authors speculated that the initial rapid reduction in aerobic capacity was due to decreased maximal Qc and circulating hemoglobin levels, while the later slow progressive component was related to muscle atrophy and impairment in peripheral gas exchange. Similarly, Greenleaf et al. (61) observed the greatest rate of decrease in VO_2max in the first week of bed rest.

Decreased aerobic capacity (28) and delayed oxygen kinetics (37) during the first one to two weeks of bed rest generally are associated with decreased circulating blood volume. However, with longer simulated microgravity exposures, structural changes in the myocardium (46;120) and the vasculature (172) may increasingly impair exercise capacity as the duration of bed rest increases. Perhonen et al. (120) suggested that cardiac compliance and filling are reduced as the bed rest duration increases beyond 2 weeks. Additionally, negative metabolic adaptations to simulated microgravity, such as reduced citrate synthase activity in skeletal muscle, become apparent after 4 weeks of unloading (10;72). Longer durations of bed rest are associated with decreased muscle mass, strength, and endurance which would be expected to impair aerobic exercise performance and decrease the efficacy of the muscle pump to protect venous return (150).

(b) Pre-Bed Rest Fitness

Taylor et al. (159) and Saltin et al. (134) were the first to report that men with a higher aerobic capacity had a greater absolute reduction in VO_2pk after bed rest than those with lower fitness. Several subsequent studies confirmed this hypothesis (38;41), but this has not consistently been the case (64). Greenleaf and Kozlowski (64) observed that this relationship was strongest when subjects performed a cycle ergometer test protocol, particularly when supine. Although they reported that the relationship was not strong during upright treadmill testing, recent data from a set of bed rest studies with twins (92;97) in which subjects performed treadmill exercise tests after 30 days of bed rest did find a significant correlation between pre-bed rest fitness and the amount of loss in VO_2pk in both male and female control (nonexercising) subjects (Stuart M.C. Lee, personal communication). However, with respect to gender, Convertino et al. (38) reported that there was a significant relationship between initial VO_2pk and VO_2pk measured after 10 days of bed rest in middle-aged (r=-0.84) and young men (r=-0.78), but not in either middle-aged (r=-0.25, NS) or young women (r=-0.38). The lack of relationship between pre-bed rest VO_2pk and the bed rest-induced loss in women in these earlier studies might be a consequence of the lower pre-bed rest VO_2pk values measured in many of these subjects and the shorter bed rest duration.

(c) Gender

Few studies have examined the effect of gender on the change in aerobic capacity after bed rest. Those that have been conducted consistently reported that although the male subjects had higher pre-bed rest VO_2pk values than their female counterparts, the loss of aerobic capacity expressed as a percentage of the pre-bed rest values was independent of gender in bed rest durations up to 30 days (Figure 16) (29;38;41;77;92;97). However, the absolute decrease in aerobic capacity ($l \cdot min^{-1}$ or $ml \cdot kg^{-1} \cdot min^{-1}$) generally is higher in males than in the female subjects.

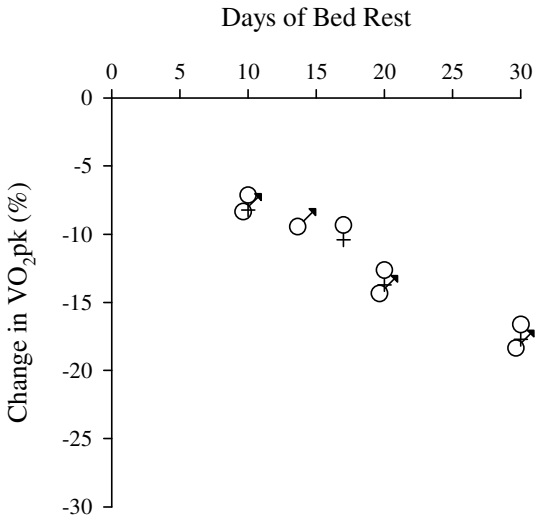

Figure 16. The percent change in aerobic capacity (VO_2pk) after bed rest is not different between men and women (97).

(d) Recovery after Bed Rest

The time course of the recovery of VO_2max following bed rest is dependent upon the recovery of the physiologic variables that contribute to maximal exercise performance. Some improvement in exercise responses is apparent within a few days of reambulation. This is largely associated with a recovery of plasma volume, which is particularly apparent during submaximal exercise. For example, the HR response to treadmill walking was significantly elevated on the first day of reambulation following a recent 60-day bed rest study but was not different than pre-bed rest 2 days later, even though VO_2pk was still significantly lower (-21%) than the pre-bed rest value (139). Although the specific recovery of post-bed rest plasma volume has not been well characterized, preliminary data from 90-day bed rest studies suggest that plasma volume on average is restored after 3 to 4 days of ambulatory recovery in non-exercise control subjects (Dr. Steven Platts, personal communication). There also appeared to be some recovery of submaximal HR, albeit less dramatic, during supine ergometry (150 W) 3 days after a 17-day bed rest period compared to the last in-bed rest test even though VO_2max was still depressed compared to pre-bed rest (-7%) (161).

Recovery of VO_2max normally occurs within 2 to 4weeks after bed rest (44), although for short bed rest durations the recovery process is well underway within one week. There was no significant difference from pre-bed rest VO_2max by 1 week following a 17-day bed rest study (-3.3%) (161), which was half the loss measured after

only 3 days of reambulation (-6.6%). A similar amount of recovery (50%) was observed in four crewmembers after a space flight of the same duration (R+8: -5.2%, R+3: -10.4%). Subjects who experience longer periods of bed rest deconditioning may require more time to reach their pre-bed rest fitness levels. Saltin et al. (134) reported that the aerobic capacity of 3 of 5 bed rest subjects who participated in 21 days of bed rest was restored within 10 to 14 days after resuming normal activities. Additionally, more fit subjects appear to return to their pre-bed rest fitness levels more slowly than their less fit counterparts (134), although the previously more highly fit subjects are likely to perform better at all time points than if they had been previously unfit.

Following 60-day and 90-day bed rest studies conducted by NASA Johnson Space Center, VO_2pk estimated from submaximal exercise tests was improved during the recovery period (from R+2 to R+11) in most subjects (Dr. Don Hagan, unpublished observations). However, VO_2pk on BR+11 was still more than 10% lower than pre-bed rest VO_2pk in 5 of the 9 subjects. All of the bed rest subjects participated in a daily 1-hour program of supervised ambulation and exercise during the post-bed rest period. The program consisted of 10-15 minutes of walking as well as calisthenics to strengthen the muscles of the trunk, upper body, and legs. The primary objective of the reconditioning plan was to restore the functional mobility and capacity to perform activities of daily living in preparation for release from bed rest. Since the protocol was not targeted specifically at increasing aerobic capacity, it is not surprising that recovery of VO_2pk was incomplete. Similarly, Sundblad et al. (156) and Spaak et al. (31) observed that submaximal heart rate still was elevated 12 and 15 days, respectively, after a 42-day bed rest, but returned to pre-bed rest levels when tested again 32 days after the end of bed rest (156). In a separate study, VO_2max of subjects was restored during the 3 weeks of ambulatory recovery when subjects performed upright cycle ergometry for 1 hour per day at 50% of VO_2max for 10 days in the last week of recovery (152).

(e) Submaximal Exercise Responses

Aerobic deconditioning after bed rest is evident by higher HR, ventilation, respiratory exchange ratio, and rating of perceived exertion during submaximal exercise (26;27;36;40;58;79;90;92;115;148;164). Of these, elevated HR during submaximal exercise is the most prominent feature of bed rest-induced deconditioning. Submaximal exercise HR was increased following 24 hours of bed rest by approximately 20 beats·min^{-1}, which Nixon et al. (115) noted was similar to the increase observed in Apollo and Skylab astronauts following space flight. Similarly, submaximal exercise HR was increased in almost every stage during supine ergometry following 14 days of bed rest, whether subjects performed a moderate intensity exercise countermeasure or not (152). During 17 days of bed rest, submaximal HR at 150 Watts was significantly increased by the eighth day of bed rest and remained elevated throughout the first post-bed rest exercise test (161). However, when subjects perform a countermeasure which preserves aerobic exercise capacity, submaximal HR is unchanged from pre-bed rest levels (78;90;92;164).

Elevated submaximal exercise HR after bed rest likely is a compensatory mechanism to maintain Qc when SV is decreased. Following 20 days of bed rest, submaximal Qc was not different during upright exercise, although HR was increased and SV was reduced in subjects performing no countermeasures (78). HR increased and stroke was

reduced when the subjects were at rest in both sedentary and endurance trained subjects following 3 days of bed rest. Although maximal SV and Qc were not measured, submaximal SV was reduced and HR was elevated only in sedentary subjects. The fact that no change was observed in endurance athletes might have been because the submaximal workloads (up to 150 W) represented a proportionally lower percentage of their maximal exercise capacity (Control: 188 W, Endurance: 270 W, Strength: 225 W) (148).

Elevated ventilation and respiratory exchange ratio may be related to a shift from fatty acids energy sources towards carbohydrates (78;90), as has been observed with normal ambulatory detraining (109;110), or to a bed rest-induced reduction in lactate threshold and/or a greater concentration of blood lactate during submaximal exercise (39;134;148;153;170). The effect of bed rest on the lactate threshold may be more apparent in more highly trained subjects, who also experience a decrease in the norepinephrine response threshold during graded exercise after short-duration bed rest (148). The impaired ability of skeletal muscle to utilize aerobic pathways after bed rest for energy utilization might be inferred from the loss of aerobic pathway enzymes (72) and reduced glucose transporter content (158), or to reduced or inappropriate distribution of blood flow, as has been observed in animal models during exercise (171). Also, the loss of buffering capacity related to a decrease in bicarbonate ions with a decrease in plasma volume and slower oxygen kinetics have been proposed to contribute to the reduction in lactate threshold. Lactate threshold is an indicator for changes in aerobic endurance capacity which may occur independently of changes in VO_2max (20), which could signal a potential for earlier onset of fatigue and impaired ability to perform sustained tasks.

2. Mechanisms of Decreased Aerobic Capacity

In ambulatory subjects, it has been postulated that the primary determinant of VO_2max is maximal Qc (127). Although the debate continues in scientific journals to this day (116;135), many have argued that the capacity of the muscular system to increase vascular conductance and oxygen consumption is greater than the ability of the human heart to pump blood (6;133). Supporting the view that maximal Qc is a primary limiting factor after bed rest, the reduction in Qc in 5 male subjects following 21 days of bed rest (-26%) was similar to the reduction in aerobic capacity (-26%) (134). Similarly, using radionuclide imaging in 12 middle-aged men, Hung et al. (74) observed a 23% decrease in maximal Qc following a 10-day bed rest, which was similar to the decrease in VO_2max (17%). However, this relationship between the decrease in maximal Qc and lower VO_2max after bed rest does not appear to remain as the duration of the bed rest is extended. Capelli et al. (22) reported that decrease in Qc after 42 and 90 days of bed rest was not significantly different than that measured after 14 days of bed rest, suggesting that peripheral factors at the level of the working muscle were responsible for further decrements in VO_2max. In contrast, Ferretti et al. (52) reported that maximal cardiac output (-31%) was reduced to a greater extent than VO_2max (-17%).

(a) Maximal HR

In general, maximal HR has been observed to be unchanged or increase slightly after bed rest (26;58), and therefore is not a contributing factor to a lower maximal Qc.

Maximal HR was unchanged following 24 hours of bed rest (115), but in a separate study was observed to increase during both supine (5.7%) and upright (5.9%) cycle exercise following a 10-day bed rest (24). Convertino (28) suggested that during these bed rest studies there was a strong inverse relationship between changes in plasma volume and changes in maximal HR, but this has not consistently been the case. In separate investigations, maximal heart was not changed after 14, 42, and 90 days of bed rest (22). Maximal HR after bed rest does not appear to be influenced by the performance of an exercise countermeasure (152), but such results have not proven to be consistent. Recently, maximal HR was unchanged in control subjects following 30 days of bed rest, but was decreased slightly, but significantly, when an exercise countermeasure was employed (92).

(b) Stroke Volume

The primary contributor to the decrease in maximal Qc, therefore, is a reduced SV. Hung et al. (74) reported that after 10 days of bed rest the reduction in Qc was solely the result of a 28% reduction in exercise SV. Similarly, maximal oxygen pulse, considered to be an index of SV, was reduced after 10 (25) and 17 days (161) of bed rest during supine ergometry, and comparable responses were noted in four astronauts following a space flight of the same duration (Figure 17) (161). Ferretti et al. (52) reported that the 31% decrease in maximal cardiac output following 42 days of bed rest was due solely to a 31% reduction in maximal stroke volume because maximal heart rate was unchanged. Resting and submaximal exercise stroke volumes also were reduced during long-duration bed rest (53;150;156) and space flight (8).

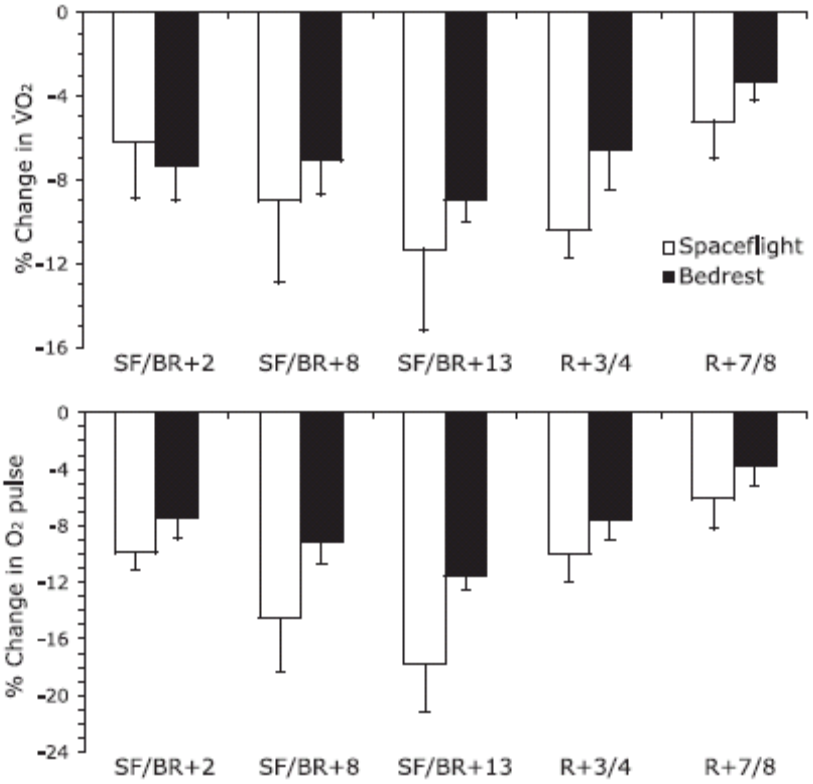

Figure 17. Oxygen consumption (VO_2) and O_2 pulse changes during exercise during and after both space flight and bed rest. Space flight data were collected at 85% of the pre-flight maximal workload, while bed rest data were collected at maximal effort (161).

Although exercise SV is reduced with bed rest, ejection fraction is increased, suggesting that ventricular performance is maintained while venous return and cardiac filling may be impaired (29). Cardiac atrophy, measured using magnetic resonance imaging, appears to occur by 14 days of bed rest, which likely contributes to reduced cardiac distensibility and smaller SV for a given filling pressure. Left ventricular mass decreased in men by 5, 8, and 16% after 2, 6, and 12 weeks of bed rest, respectively (120). Additionally, left ventricular end-diastolic volume decreased by 14% after 2 weeks of bed rest but changed only minimally thereafter. Similar observations were made in women after 60 days of bed rest (46).

(c) Venous Return

Decreased venous return may be the result of an increase in lower body venous compliance and reduced plasma volume that has been commonly observed after bed rest (29). Although multiple vascular factors contribute to limb compliance, changes in muscle mass and tonicity associated with bed rest may contribute to increased venous pooling when the mechanical obstruction to venous stretching and accumulation of blood is reduced. Following 30 days of bed rest, calf compliance was increased (2.4%) concomitant with a decrease in muscle volume (-5%) (33). In this bed rest study, changes in muscle cross-sectional area explained approximately 50% of the variability in the change in calf compliance. When subjects are exercising, it is recognized that cardiac filling pressure, SV, and Qc are supported by the expulsion of blood from the active

muscles by the "muscle pump," but these mechanisms will be of little importance in non-active muscles and other compliant regions of the circulation.

Blood may pool in other areas of the body after bed rest, including the splanchnic region, which would affect venous return during exercise. Savilov et al. (136) used radioisotope tracers to measure translocation of blood during LBNP, an orthostatic stressor. Subjects with low orthostatic tolerance displayed a marked increase in blood pooling in the abdomen during LBNP, with reflective decreases in blood distribution to the head and chest. Subjects with relatively better LBNP tolerance had less extreme responses. Similarly, Fischer et al. (54) reported that splanchnic blood flow was higher at each level of LBNP following just 4 hours of bed rest, and this was associated with an increased heart rate and reduced stroke volume.

The reduction in vasoconstrictive reserve that Convertino and Cooke (32) suggest as a factor in orthostatic intolerance after bed rest and space flight also may contribute to reduced exercise capacity. Following 16 days of bed rest, elevated vasoconstriction was evident at rest in response to reduced plasma and SVs (49), and maximal vascular resistance was unchanged but was achieved at a lower level of orthostatic stress induced by a graded lower body negative pressure protocol (30). An inability to vasoconstrict – particularly in the venous system, which contains 70% of the total blood volume of a resting subject – impairs the ability to compensate for decreased blood and plasma volume, especially when coupled with orthostatic stress, to maintain venous return and SV during exercise.

Linked to this, changes in sympathetic nervous system response to exercise may be important to maximal exercise capacity with regard to the appropriate distribution of blood flow. Specifically, there is an inverse relationship between norepinephrine concentrations and splanchnic blood flow. Rowell (127) calculated, for example, that regional vasoconstriction in the splanchnic organs, kidneys, and skin can provide an additional 600 ml of O_2 per minute at maximal exercise in normal ambulatory subjects. Elevated levels of circulating norepinephrine may be an important adaptation to reduced blood volume to defend muscle blood flow and restrict flow to the splanchnic region and other inactive tissues (47). Sympathetic nervous system activity and catecholamine levels in resting subjects have been reported to be either unchanged or decreased following bed rest, and elevated HR in resting subjects has been ascribed to reduced vagal control (29). Following 3 days of bed rest, the norepinephrine levels during submaximal exercise tended to be higher and the norepinephrine threshold was lower in endurance athletes following bed rest, but these alterations were not evident in sedentary subjects (148). There was, however, no difference in maximal norepinephrine concentrations or epinephrine responses in either group. In contrast, following 16 days of bed rest, Engelke and Convertino (47) reported that plasma norepinephrine concentrations were 64% greater at peak exercise although peak heart was only 5% higher. However, no changes in epinephrine were reported during rest or maximal exercise.

(d) Plasma Volume

Previous investigations consistently have demonstrated that plasma volume is rapidly reduced during exposure to space flight and bed rest, with the majority of the initial loss occurring within 1-2 days (16). Plasma volume has been observed to be decreased in as

little as 6 hours, reaching a 10% loss in 24 hours (115), and equaling approximately 12% by the third day of bed rest. Greenleaf et al. (62) have suggested that the loss of plasma volume is progressive through 60 to 80 days of bed rest. The time course of the decrease in plasma volume is similar to the decrease in exercise capacity (Figure 18), and the mean loss of plasma volume across studies has been reported to account for approximately 70% of the variability in the mean decrease in VO_2max following up to 30 days of bed rest (29). Reduced circulating plasma volume may negatively affect exercise SV, the delivery of oxygen and nutrients to working muscle, and the removal of metabolic waste products. Thus, preservation of plasma volume has been suggested to be an important factor in the maintenance of exercise capacity during bed rest, and may be even more important during upright than supine exercise because of the addition of gravitational stress.

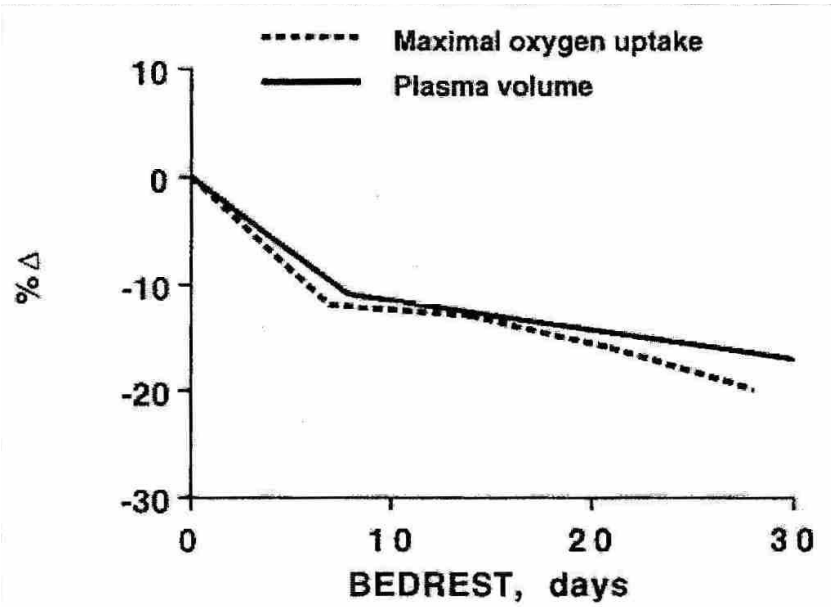

Figure 18. Decreased maximal oxygen consumption in subjects who perform no countermeasures appears to parallel losses of plasma volume up to 30 days of bed rest (29).

Maintenance of plasma volume alone is likely not the only determinant of exercise capacity preservation, especially following longer duration bed rest studies. Blomqvist et al. (17) provided sufficient amounts of saline through infusion to restore the central venous pressure to the pre-bed rest levels following a 24-hour bed rest. Although this procedure was not protective of orthostatic tolerance, it did abolish the loss of upright exercise capacity. However, Stremel et al. (152) maintained plasma volume (-8%, NS) in subjects during 14 days of bed rest by employing two daily 30-minute bouts of supine cycle exercise at 68% of pre-bed rest VO_2max, but supine VO_2max (-9%) and submaximal exercise responses were not maintained. In addition, subjects who performed an isometric exercise regimen during the same study experienced loss of plasma volume that was similar to the non-exercise control subjects (-15% vs. -10%), but the decrease in aerobic capacity was not as great (-5%) in the isometric exercise group. In a separate study, restoration of plasma volume at the end of a 16-day bed rest following an intense exercise bout did not successfully maintain maximal aerobic capacity (48).

When reporting the results of plasma volume and maximal exercise capacity for individual subjects, the relationship between these two outcomes may not be as strong as when comparing mean results for a group of subjects. In general, there appears to be more variability in the plasma volume response to bed rest than in the decrease in VO_2max. Additionally, as the duration of the bed rest period increases, the strength of the relationship appears to decrease. Following 14 days of bed rest, in control subjects and subjects participating in a countermeasure employing a reverse pressure gradient garment, the decrease in VO_2max was significantly related to the loss of plasma volume (r^2=0.56) (40). Recently, in a study of male control and exercise countermeasure subjects, the change in plasma volume from pre-bed rest accounted for only 24% of the variance in upright exercise capacity after 30 days of bed rest (92). In a companion study utilizing female control and exercise subjects, there was no significant change in plasma volume in either the control or countermeasure subjects although the control subjects experienced a significant loss of aerobic capacity while the countermeasure subjects did not. The lack of change in plasma volume in both the female control and exercise subjects appears to support previous observation that exercise capacity is not strongly related to the change in plasma volume with bed rest (139).

(e) Arteriovenous Oxygen Difference

Maximal systemic oxygen extraction, assumed to be at the level of the working muscle, does not appear to be affected by short-duration bed rest. There was little change in arteriovenous difference in middle-aged men following 10 days of bed rest (74), and it was unchanged after 21 days of bed rest in five male subjects (134). In general, the maximal extraction of oxygen from the systemic circulation does not appear to be specifically affected by bed rest, but oxygen extraction during submaximal exercise appears to be increased to compensate for the lower hemoglobin concentration during longer durations of bed rest (53). However, it is not clear from these data whether blood flow is appropriately directed to working muscle and whether the extraction at the level of muscle itself is maintained.

Delivery of oxygen to the muscle has been suggested to be impaired after bed rest. Resting leg blood flow (15), and(48) peak vascular conductance (34), which has been associated with VO_2 max in ambulatory subjects (81;101;124;149), are reduced following bed rest. The reduction in vascular conductance was associated with a decreased resistance to fatigue of the calf muscle, but when peak vascular conductance was restored with a maximal bout of exercise at the end of bed rest VO_2max was not similarly protected (48). However, peak vascular conductance was associated with VO_2max before and after bed rest, suggesting that protection of peripheral mechanisms associated with the oxygen utilization in the muscle are not effective unless central cardiac effects are restored (48). Additionally, Hikida et al. (72) reported a 37% decrease in the capillary-to-fiber ratio of the soleus following 30 days of bed rest, although Ferretti et al. (51) observed no change in either capillary density or capillary-fiber ratio in the vastus lateralis.

(f) Decreased Red Blood Cell Mass

Red cell mass has been reported to be decreased in as little as 7 days of bed rest (36), although most consistent results are observed at bed rest day 14 (58), and red cell mass

may continue to decline for a short period during the recovery from bed rest (58;93;141). Convertino et al. (40) reported that red cell volume was decreased by 11% during 14 days of bed rest, independent of whether the subject performed no countermeasures or participated in a protocol to simulate the effects of orthostatic stress. Exercise during bed rest may prevent the loss of red cell mass; however, exercise that is too intense has the potential to cause red cell destruction (58).

The correlation between the change in red cell mass and the change in VO_2max is low in short- and moderate-duration bed rest studies (29), and changes in aerobic capacity can be observed during short-duration bed rest studies even without a measurable change in red cell mass (39). In general, hematocrit does not change during bed rest, suggesting that the oxygen carrying capacity per unit of blood is unchanged (29;40). However, as red cell mass continues to decline with longer bed rest, albeit at a slower rate (119), the total oxygen delivery capacity of the blood is reduced at rest and during submaximal exercise (53) and further impaired at maximal exercise when maximal Qc also is reduced (52). Capelli et al. (22) reported that hemoglobin concentration was decreased by 9% after 42 days of bed rest, which along with the decrease in Qc was reflected in a 34% decrease in total oxygen delivery. However, arterial saturation of hemoglobin was unchanged during bed rest (22;52).

(g) Cerebral Perfusion

Inadequate cerebral perfusion during post-bed rest exercise also might impair exercise performance, particularly when performed against an orthostatic stress. Prior to 30 days of bed rest, the majority of subjects terminated graded exercise tests due to general fatigue and shortness of breath (92). After bed rest, half of the control subjects who performed no countermeasures reported lightheadedness or loss of balance as the primary reasons for test termination. In contrast, fatigue and shortness of breath remained the predominant symptoms at test termination after bed rest in a group of subjects who performed an exercise countermeasure which maintained VO_2pk.

Reduced exercise capacity after bed rest also may be related to changes in central command. The strength of voluntary maximal muscle contraction is reduced to a greater extent (-36%) than muscle tension which is electrically-evoked (-24%), and the difference between these two muscle tensions, termed the force deficit, increased by 40% during bed rest (80). If muscle performance is inhibited in this manner following a period of unloading, VO_2max and Qc, according to the "oxygen pull" model, consequently also would be reduced (116). Inadequate cerebral blood flow and local brain ischemia may further exacerbate this.

3. Other Contributing Factors Influencing Aerobic Exercise Performance

(a) Orthostatic Stress

The influence of gravity on work performance is apparent when comparing results from supine versus upright exercise capacity after equal durations of simulated microgravity. After short duration bed rest, VO_2max decreased 2-2.5 times more during upright exercise compared to supine exercise (24;36). After 10 days of bed rest in middle-aged men, the reduction in VO_2max was 15% in the upright posture, but was only 6% (N.S.) when subjects were tested in the supine posture (24). Submaximal exercise

responses are similarly affected; at the same absolute work intensity (115 Watts) pre- and post-bed rest, HR was elevated by 4% above pre-bed rest values when subjects performed supine ergometry, but was increased by 8% when the exercise was performed upright. Exercise in the upright posture is associated with a greater reduction in SV and Qc than supine exercise. Saltin et al. (134) reported that both resting and exercise SVs were reduced to a greater extent when subjects were upright (Rest:-24%, Exercise: -35%) than when the subjects were supine (Rest: -17%, Exercise: -23%).

Exercise alone prevents the loss of aerobic capacity when pre- and post-bed rest tests are performed in the supine posture. Similarly, in-flight exercise capacity is maintained by in-flight exercise during short- and long-duration space flight when crewmembers are not exposed to orthostatic stress. However, the maintenance of upright exercise capacity is more relevant to Space Shuttle and ISS crewmembers who may be required to egress without assistance from the Shuttle in an emergency, or during exploration missions when work in an extravehicular suit in a partial gravity field, shortly after planetary landing, may be integral to mission success (90;164). Emergency egress from the Shuttle represents a significant metabolic (>2.5 $l \bullet min^{-1}$) and cardiovascular (>160 $beats \bullet min^{-1}$) stress in normal ambulatory subjects (14) and would be a much greater challenge after long-duration ISS missions that typically last six months or more.

A potential relationship between the preservation of orthostatic tolerance and exercise performance by implementation of a single countermeasure would be an attractive feature to NASA. During recent studies utilizing exercise and LBNP as an orthostatic stressor, the countermeasure subjects maintained aerobic capacity (92;164) and experienced smaller bed rest-induced changes in cardiovascular responses during subtolerance orthostatic stress (140) and attenuated orthostatic intolerance (166). Using these data to specifically link orthostatic tolerance and exercise capacity is weakened when relying upon these data sets alone because the countermeasure is a combination of exercise and orthostatic stress. However, data from Space Shuttle missions suggest that crewmembers who perform more exercise during space flight experience less change in aerobic capacity (59) and smaller increases in HR during standing (91).

(b) Thermoregulatory Changes

Physical work capacity after bed rest and space flight may be further reduced by impaired body temperature regulation during rest and exercise that, in turn, may lead to heat strain and injury. With regard to space flight, the combined effects of plasma volume loss and loss of heat acclimation may result in excessive heat strain for crewmembers wearing protective garments during launch and landing (118). During a nominal landing (STS-90, April 1998) prior to exit from the Space Shuttle, intestinal temperature (core temperature) was significantly elevated in four crewmembers wearing the required Launch and Entry Suit (LES) despite the use of a liquid cooling garment (125). In the event of an emergency egress from the Shuttle, crewmembers would be disconnected from the thermoelectric cooling unit supplying the liquid cooling garment in order to exit the vehicle; and they would then be required to ambulate to a safe distance. This activity would be completed fully suited and may require an effort in excess of 70% of the crewmember's preflight VO_2pk (14). The combined thermal load of the protective garment and the elevated metabolic rate during egress would be expected to rapidly increase core temperature.

Impaired thermoregulation at rest and during exercise is evident after bed rest. Crandall et al. (42) passively heated subjects with a warm water-perfused suit before and after 15 days of bed rest. After bed rest, these subjects had a reduced forearm blood flow and vascular conductance both before and during whole body heating as well as an increased oral temperature threshold at which forearm vascular conductance increased in response to the heat stress. Michikami et al. (106), using similar techniques, also observed an increase in the threshold temperature and decreased sensitivity of the vascular conductance and sweating response following 14 days of bed rest. A higher core temperature has been observed during submaximal exercise in both warm (55) and temperate (65;93) conditions, with changes occurring in as little as 24 (50) to 72 hours (148). The elevated post-bed rest core temperature during exercise was ascribed to a decreased ability to increase skin blood flow (60;93) (Figure 19) but also may be related to impaired sweating responses (65;93). However, the performance of an exercise countermeasure during bed rest has been shown to prevent these deleterious adaptations (43;143). This exercise countermeasure protocol also was demonstrated to preserve maximal aerobic capacity.

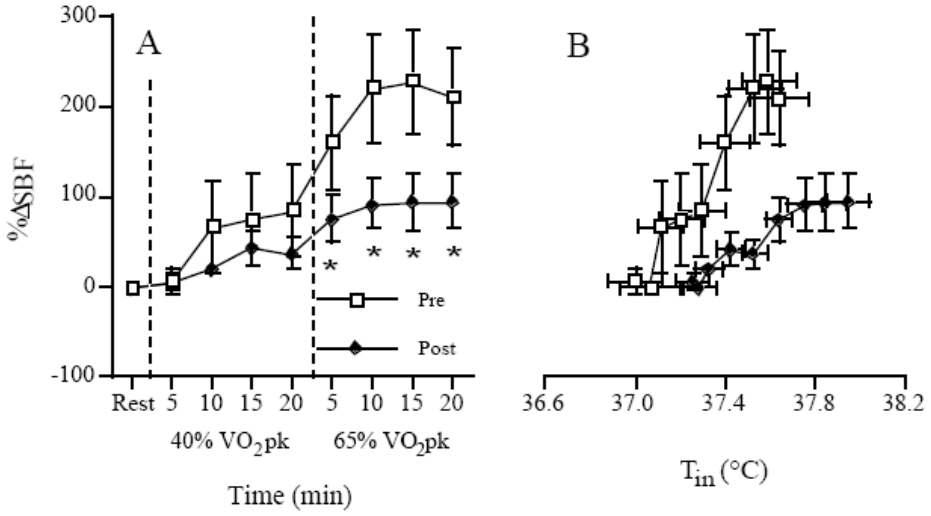

Figure 19. The change in skin blood flow in response to increasing core temperature during submaximal exercise is reduced after bed rest (Panel A). The onset of the vasodilatory response was delayed and the slope of the response tended to be reduced (Panel B) (93).

Changes in thermoregulatory control may be impacted during and after space flight. Leach et al. (88) reported that evaporative water loss was reduced by an average of 11% in 9 Skylab crewmembers during their in-flight exercise as compared to preflight. The authors suggested that the sweating responses may have been reduced in the microgravity environment through the formation of a film of sweat on the surface of the skin, because of reduced sweat dripping, which impaired air flow across the skin and sweat evaporation. Further, reduced gravity would have impaired spontaneous convection, in which air rises or falls due to differences in density (117), and low air flow in the cabin of space vehicles during space flight may limit heat loss capacity (56).

Fortney et al. (57) observed that the thermoregulatory mechanisms were severely impaired in two crewmembers when performing exercise following long-duration space flight (115 days) onboard the Mir space station. Both crewmembers had mildly elevated

core temperature at rest and after 20 min of exercise at 40% VO_2pk, and each had a delayed onset of sweating rate response and skin vasodilation. Neither crewmember was allowed to complete the second exercise stage postflight (20 minutes at 65% pre-flight VO_2pk); the flight surgeon terminated the test "due to an excessive rise in HR." Despite the shortened exercise time, both crewmembers had a core temperature at the end of the postflight exercise bout similar to the core temperature at the end of the entire exercise protocol during pre-flight testing. Both crewmembers exhibited lower skin blood flow and sweating rate responses that may have contributed to this elevated core temperature.

4. Countermeasures

The optimal countermeasure prescription for the prevention of space flight-induced deconditioning should ideally include components to stimulate or maintain each organ system's condition similar to that maintained in a normal gravity environment (163), and it should require a minimal amount of crewmember time. The total time currently allowed for resistive and aerobic exercise on ISS, including set-up and stowage of the exercise hardware, and personal hygiene, is only 2.5 hours per day. Countermeasures that are too long or too intensive may reduce compliance in some crewmembers and may be difficult for schedulers to accommodate among various mission critical tasks (92). It is paramount that the countermeasures employed to protect crew health be of sufficient efficacy to promote and maintain high levels of function, such as aerobic and anaerobic fitness, in both male and female astronauts. As of 2001, 22% of the active astronaut corps was women (71), and the proportion of female astronauts may continue to increase. Care must be taken, however, when attempting to implement countermeasures that were successful in bed rest to the space flight environment due to logistical constraints of the space flight environment. In addition to crew time, exercise hardware mass, volume, and stowage should be considered as well as the impacts of countermeasure performance on the environmental control systems.

Although the preservation of aerobic capacity and exercise performance after short-duration bed rest studies primarily may be achieved through protecting against blood volume losses and changes in SV, the maintenance of exercise capacity during longer bed rest exposures also likely requires the maintenance of aerobic pathway enzymes (72), muscle strength and endurance, neuromuscular coordination, muscle capillary density, and cardiac mass and function (46;120). However, relative hypovolemia may exacerbate the effects of other bed rest-induced adaptations during upright exercise above that experienced during supine exercise because of the translocation of blood below the hydrostatic indifference point with the addition of orthostatic stress.

(a) Exercise

Exercise is a natural modality to consider when developing countermeasures to the decrease in aerobic capacity during and after bed rest. Moderate intensities of aerobic exercise are not consistently effective to prevent the loss of aerobic capacity (157). Stremel et al. (152) were unable to prevent the decrease in aerobic capacity during two weeks of bed rest when subjects performed two 30-minute bouts of supine cycle ergometry daily at an exercise intensity of 68% of pre-bed rest VO_2max. However, Shibasaki et al. (143) maintained aerobic capacity in a longer bed rest study (18 vs. 14 days) by increasing the total exercise time from 60 to 90 minutes at 75% pre-bed rest HR. By extending the length of the exercise countermeasure, plasma volume also was

maintained (-2%, NS), while it was significantly decreased (-12%) in the shorter study (152).

Short, intense bouts of exercise in ambulatory subjects are considered to be more effective than longer, less strenuous exercise in promoting changes in aerobic fitness in ambulatory subjects (167), and therefore are perhaps more likely to provide protection during bed rest. Greenleaf at al. used a near maximal (up to 90% of pre-bed rest VO_2max) interval exercise, two 30-minute bouts, 5 days per week during a 30-day bed rest, to prevent the loss of both exercise capacity (61) and plasma volume (-1%, NS) (66). Control subjects in this study experienced an average decrease in VO_2max of 18%, but the subjects experienced no change in exercise performance (+3%, NS). The success of this protocol in bed rest prompted NASA Astronaut Strength, Conditioning, and Rehabilitation Specialists to include this protocol in their exercise prescriptions for astronauts onboard the ISS (Dr. Alan Moore, personal communication), and similar exercise countermeasure protocols have been used successfully in bed rest studies by other investigators (78;90;92;164).

In an attempt to develop a more time efficient exercise countermeasure protocol, Convertino et al. (25) had subjects perform a maximal bout of supine cycle ergometry as a simulation of exercise in microgravity at the end of a 10-day bed rest. Although VO_2max measured during this supine ergometry test was significantly reduced from pre-bed rest (-5.6%), when subjects performed an upright treadmill test 3 hours later, they exhibited no change in treadmill VO_2max compared to the pre-bed rest measurement. However, a single bout of intense exercise 24 hours before resumption of normal ambulatory activities which normalizes plasma volume (control: -16%, exercise: -4%, NS) (35) and protects LBNP tolerance (49), does not prevent a decrease in aerobic capacity (48). It has been postulated that factors other than the exercise countermeasure, including readaptation to the upright posture (61), likely influenced the preservation of treadmill exercise capacity observed in the earlier study.

Decreased muscle strength and endurance associated with bed rest deconditioning (58;89;111;112;142) also likely affect maximal exercise performance, particularly during cycle ergometry testing when knee extensor muscles are greatly involved. For example, decreased local muscle fatigability in the calf muscles following 16 days of bed rest was correlated with a decrease in VO_2max among control subjects (48). However, few studies have directly assessed the use of a resistive exercise countermeasure to protect aerobic exercise capacity. Stremel et al. (152) reported that subjects who performed two 30-minute sessions of static leg extension exercise (21% MVC for one minute followed by one minute of rest) during a 14 day bed rest study experience a significant decrease in aerobic capacity (-4.8%), but the loss appeared to be attenuated compared to both control subjects (-12.3%) and those subjects who had performed a moderate intensity aerobic exercise countermeasure (-9.2%). Similarly, when subjects in a 30-day bed rest study performed two 30 minutes bouts of maximal isokinetic exercise (10 seconds of work, 50 seconds of rest,15 minutes per leg) supine VO_2max was not preserved (-9.1%) but the loss was half that experienced by the control subjects (-18.2%) (61). This partial preservation of aerobic capacity using resistive exercise alone suggests that muscle strength and endurance are significant contributors to aerobic exercise performance after bed rest. Additionally, other studies which have used aerobic exercise countermeasures

to prevent the decreased VO_2max following bed rest demonstrated a protection of muscle performance (1;92;166).

(b) Artificial Gravity

The concept that gravitational or gravitational-like stress alone will provide some protection against the decrease in aerobic capacity associated with bed rest is not new. In the 1960s, several reports were published which suggested that the amount of deconditioning associated with chair rest was less than that observed following strict bed rest (13;84;85). Later work demonstrated that exposure to a real or simulated orthostatic stress alone may attenuate the loss of upright aerobic capacity during short-duration, but perhaps not longer duration, bed rest studies. Four hours of quiet standing (163) or 3 hours of peripheral fluids shifts induced by a reverse pressure gradient garment (40) were partially effective in protecting exercise capacity during 4 and 15 days of bed rest, respectively. In contrast, subjects who were exposed to two 30-min sessions of centrifugation (+2Gz) daily during 4 days of bed rest or daily multiple bouts of LBNP (-35 mmHg) during one month of bed rest experienced a similar loss of upright aerobic capacity as control subjects (75;126). These findings suggest that long-duration or more frequent exposures to orthostatic stress alone are necessary to protect against decreased post-bed rest exercise capacity.

Recently, NASA completed a 21-day bed rest study in which 15 male subjects were assigned to serve as controls or to receive an artificial gravity countermeasure generated by a short radius human-rated centrifuge (Dr. Alan Moore, unpublished results). Countermeasure subjects were exposed to 1 hour of artificial gravity per day, with a load equivalent to +2.5 G_z at the feet. The subjects performed upright cycle ergometer tests to measure VO_2pk before bed rest and on the first day of recovery. VO_2pk was reduced by 10% in the control group, but was not significantly changed in the subjects who received the artificial gravity countermeasure (-6%, NS; Dr. Alan Moore, personal communication). Following bed rest, plasma volume was reduced (-9%) in both control and countermeasure subjects, and there were no differences between the groups (Dr. Michael Stenger, personal communication). However, the knee and ankle extensor muscle strength of the countermeasure subjects was superior to that of the control subjects, perhaps because the countermeasure subjects performed short range of motion knee bends and heel raises during the centrifugation to protect against presyncope (Dr. Vince Caiozzo, personal communication), which may have aided in the performance of cycle test after bed rest.

(c) Combination Protocols

Protection against the loss of aerobic capacity after bed rest is probably most effective when the simulated or real upright posture is coupled with exercise. The combination of orthostatic stress and even mild exercise reduces the countermeasure time requirement in bed rest by one half to produce a similar benefit (163). The addition of a gravity-like stress during exercise training may be necessary to maintain upright exercise responses after space flight and bed rest (36). Supine exercise may maintain plasma volume (66), but a gravitational component, real or simulated, may be required to maintain venous return and SV during post-bed rest exercise.

Centrifugation to simulate an orthostatic stress during cycle exercise has been successfully employed to maintain upright exercise capacity (Figure 20) (78). Subjects who performed two 20-minute sessions of combined exercise and centrifugation on alternating days of 20 days of bed rest maintained upright exercise capacity (-9±7%, NS), while those who did not perform the countermeasure experienced a significant loss (-27±7%). Countermeasure subjects exercised first for 20 minutes with a 0.8-1.4 Gz load at the heart while pedaling the cycle ergometer with a constant exercise intensity of 60 Watts. A 10 minute rest period without exercise or centrifugation was then permitted before subjects began the second exercise session. Subjects experienced 0.3 g at heart level during this session and performed an interval exercise protocol similar to one which had been previously used to preserve upright exercise capacity during 14-days of bed rest (164). In addition to protecting VO_2max, cardiopulmonary responses to submaximal exercise, including HR and SV, were maintained in subjects performing exercise during centrifugation.

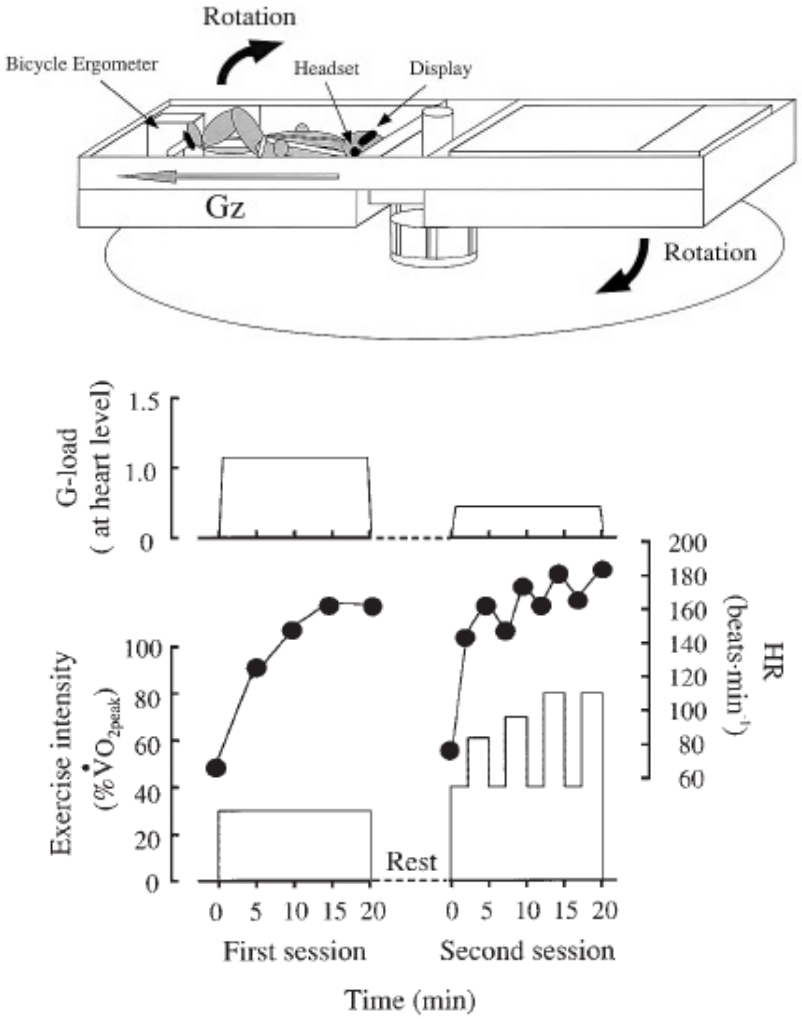

Figure 20. Centrifuge with cycle ergometer and the countermeasure protocol utilized by Katayama et al. (78) to preserve upright exercise capacity.

Technical and logistical barriers to continuous whole space craft rotation or intermittent short-radius centrifugation currently exists which make near term utilization of this centrifugation difficult, and therefore using lower body negative pressure (LBNP) to simulate orthostatic stress during an exercise may be an attractive alternative. The use of LBNP and exercise in separate sessions during bed rest was examined during a 28-day bed rest in which countermeasure subjects participated in a protocol of light supine cycle and isokinetic exercise throughout bed rest and LBNP (-40 mmHg for 15 minutes per day) in the latter half of a 28-day bed rest. Countermeasure subjects appeared to receive some protection against loss of aerobic capacity (-6% vs. Control: -16%), although the authors stated that this difference was "near the defined limit for statistical significance ($p=0.06$)" (73). Also, plasma volume was maintained in the countermeasure subjects but significantly reduced in the control group (100).

Concurrent treadmill exercise during LBNP (Figure 21) was developed over the past two decades (68-70) by a team of investigators led by Dr. Alan Hargens and Dr. Suzanne Schneider. The concept was developed in response to reports that long-duration crewmembers aboard the Mir space station exercise on the treadmill using loads equivalent to 60-70% of pre-flight body mass (168), which likely contributed to the inability of exercise countermeasures to fully prevent reduced aerobic capacity (107), bone loss (147), postflight orthostatic intolerance (103), and decreased muscle mass, strength, and endurance (94). Over the past decade the investigator team has documented the safety and effectiveness of a combined LBNP and treadmill exercise countermeasure. This integrated countermeasure method combines high loads on the musculoskeletal system with upright, Earth-like distributions of transmural pressure across blood vessels (69). Subjects participating in these studies have comfortably run on the treadmill for up to 40 minutes daily at up to 1.2 body weights (~60 mm Hg) and experience dynamic loading with inertial forces on the musculoskeletal and cardiovascular systems similar to those present during upright exercise on Earth (113;114). In fact, metabolic and biomechanical responses of treadmill exercise within LBNP during simulated microgravity are comparable to metabolic and biomechanical responses of upright treadmill exercise on Earth (18). The LBNP and exercise countermeasure system has prevented reductions in maximal aerobic capacity, altered submaximal exercise responses, and decreased sprint performance (90;92;97;139;164) during 5, 15, 30, and 60 days of bed rest.

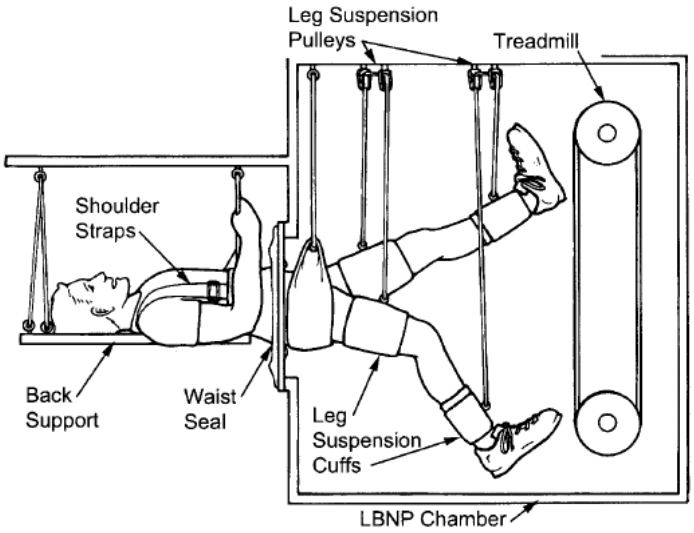

Figure 21. Illustration depicts the lower body negative pressure. This (LBNP) exercise device used for supine treadmill exercise during bed rest durations of 5, 15, 30, and 60 days (90;92;97;139;164). The device consists of a vacuum control system connected to a LBNP chamber enclosing a vertically oriented treadmill. A suspension system allowed subjects to perform treadmill exercise while supine by supporting their back and legs against the downward force of gravity. A broad, flexible neoprene waist seal spans the area between the subject and the edge of the elliptical opening. The waist seal area was to equal twice the subject's waist cross-sectional area, such that the negative pressure necessary to produce one body weight equaled -50 to -60 mmHg.

The LBNP and exercise device was first tested in a five-day bed rest study (90). Countermeasure subjects performed an interval exercise protocol which was modeled after one which successfully prevented a decrease in supine aerobic capacity (61) and protected plasma volume (66) during 30 days of bed rest. The LBNP and exercise subjects exercised daily for 30 minutes against LBNP which provided one body weight of loading (mean: -51 mmHg). After the exercise, both the upright and LBNP and exercise subjects stood (LBNP and exercise subjects experienced LBNP without exercise) for 5 minutes. The length of the bed rest was insufficient to observe a consistent change in upright VO_2pk in the control group, but the submaximal exercise HR, respiratory exchange ratio, and ventilation were elevated. These changes during submaximal exercise were not evident in the LBNP and exercise group. LBNP and exercise training also prevented a decrease in plasma volume, which was observed in the control group, and protected against a decrease in tolerance to 30 minutes of head-up tilt (165).

The LBNP and exercise countermeasure was tested again during 15-days of bed rest in seven subjects using a cross-over design (164). The exercise protocol was modified by increasing the duration of the high work stages (3 vs. 2 minutes) and the total exercise time (40 vs. 30 minutes), but the target intensities were somewhat less than in the 5-day study (peak intensity 80% vs. 90% pre-bed rest VO_2pk). The post-exercise LBNP exposure was not utilized in this project, but the amount of loading provided by LBNP was increased during the study to subject tolerance (1.0-1.2 body weight). When serving as controls, subjects experienced a significant decrease in aerobic capacity (-14%), but had no significant change in aerobic capacity after bed rest when they performed the LBNP and exercise countermeasure 6 days per week (-5%; Figure 22). Muscle performance also appeared to have been protected by this countermeasures; the time

required to sprint 27.4 meters and plantarflexor muscle strength were maintained in the countermeasure subjects, while sprint time increased and plantarflexor strength decreased in the control condition. Additionally, the countermeasure attenuated the post-bed rest decrease in orthostatic tolerance, as measured using a progressive LBNP protocol, compared to the losses experienced by the control subjects (140).

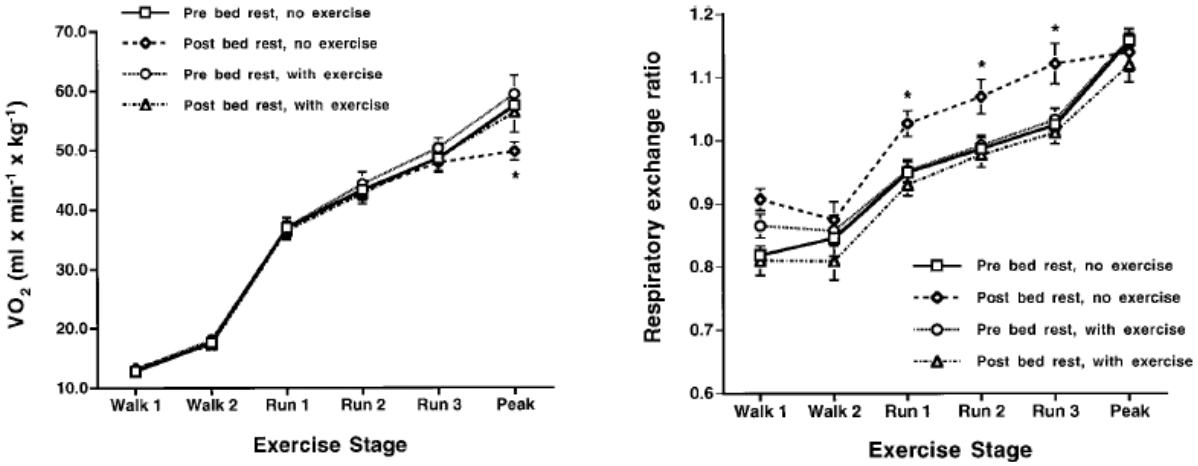

Figure 22. Submaximal and maximal oxygen consumption (VO_2) and respiratory exchange ratio before and after 15 days of bed rest with and without an LBNP and exercise countermeasure (18).

The LBNP and exercise countermeasure was later tested in male and female twins, one serving as the control and the sibling serving as the countermeasure subject, during 30 days of bed rest (92;97). The countermeasure protocol was the same as used in the 15-day bed rest study (164), except that the post-exercise LBNP exposure utilized in the 5-day study (90) was reinstated (Figure 23); the investigative team hypothesized that the post-exercise orthostatic stress when the skin and muscle bed were near maximally dilated were helpful in preserving orthostatic tolerance (140;166). Aerobic capacity was decreased in the control subjects after bed rest (-18%), but not in the LBNP and exercise subjects. The time required to sprint 30.5 meters and knee, ankle, and trunk extensor muscle strength also were maintained in the countermeasure subjects, but not in the controls (21;138), Performance of the LBNP and exercise countermeasure protocol also attenuated the decrease in orthostatic tolerance (166). During head-up-tilt at sub-tolerance levels of orthostatic stress, SV and HR during head-up tilt were maintained after 30 days of bed rest in the countermeasures subjects.

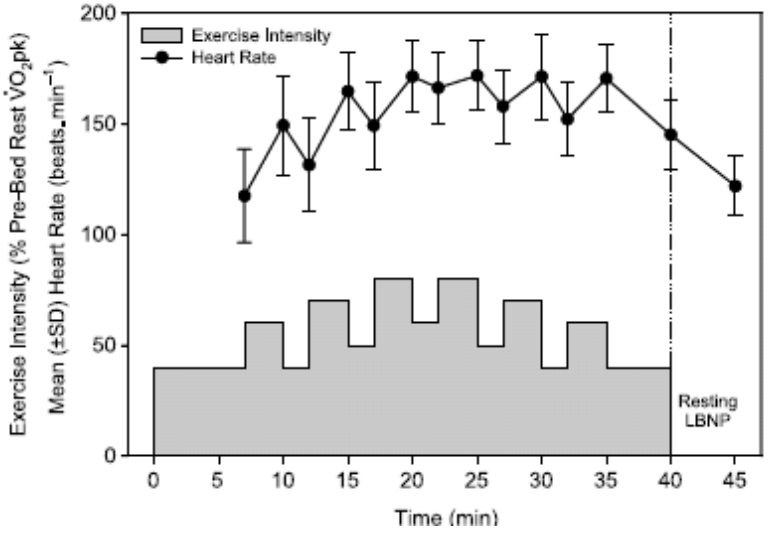

Figure 23. Mean HR response to the exercise countermeasure sessions performed by the male countermeasure (exercise plus LBNP) subjects during 30 days of bed rest from (92).

Most recently, the LBNP and exercise countermeasure was tested during 60 days of bed rest (WISE-2005: Women's International Space Simulation for Exploration), in which countermeasure subjects also performed a resistive exercise protocol. Countermeasure subjects performed the LBNP and exercise protocol an average of 3 days per week and performed supine leg press and calf press on alternate days. The same exercise protocol as in the 15- (164) and 30-day bed rest studies (92) was utilized during LBNP and exercise sessions, but the duration of the post-exercise LBNP stress was increased to 10 minutes. The resistive exercise protocol was fashioned after a countermeasure protocol which was successful in preserving muscle strength and volume in male subjects during 29 and 90 days of bed rest (3;4). During a treadmill walking test on the first day of recovery, submaximal exercise responses were preserved in the countermeasure subjects but were elevated in the controls. When a maximal treadmill exercise test was conducted on the third day of recovery, VO_2pk in the countermeasure subjects was not different than pre-bed rest (-3%, NS), although VO_2pk was significantly decreased in the control subjects (-21%). Unlike previous work, sprint performance was not tested in this study, but ventilatory threshold was determined to be preserved in the countermeasure subjects and decreased in the controls. Knee extensor muscle strength and endurance (95) and ankle extensor strength (162) also was preserved with this countermeasure. Additionally, LBNPex plus resistive exercise prevented cardiac atrophy in women during a 60-day bed rest (46). Left ventricular volume and long axis length was maintained in the countermeasure subjects during bed rest, and left ventricular mass, right ventricular mass, and mean wall thickness increased in these subjects.

Unfortunately, presumably due to the large budgetary requirements of performing bed rest studies with multiple groups, none of the investigations which have used a countermeasure combining orthostatic stress and exercise have utilized either a group who were exposed to orthostatic stress alone or exercise alone. Consequently, it is impossible to determine the proportional contributions of the countermeasure

components, exercise alone, orthostatic stress alone, or their combination, on post-bed rest exercise performance.

5. Bed Rest Data Summary

The decrease in aerobic capacity during bed rest is rapid, occurring in a similar fashion as the loss of plasma volume during the first two weeks of bed rest. Thereafter, decreased VO_2pk in response to bed rest progresses in a less steep rate of decay and appears influenced by central and peripheral adaptation. Ferretti et al. (52) have suggested that following long-duration bed rest, 73% of the reduction in VO_2max can be explained by decreased oxygen transport from the lungs to the muscles, with the remaining influences equally divided between the oxygen diffusion and utilization at the cellular level. Bed rest investigations have demonstrated that frequent (at least 3 days per week), short bouts of intense exercise (interval-style and near maximal) during the bed rest period provides a time efficient level of protection against this form of cardiopulmonary deconditioning and also may safeguard against negative adaptations in other organ systems. Although exercise without orthostatic stress may be beneficial, complete protection against changes in upright exercise performance may be best realized when exercise is undertaken in combination with an orthostatic stressor as provided by centrifugation or LBNP.

V. Computer-Based Simulation Information

Since VO_2max is primarily determined by Qc, we would expect any factors related to heart function or plasma fluid would be of functional significance. The impact of the microgravity induced changes in both plasma volume and diastolic function are integrated into the operation of the Digital Astronaut as noted in the graphic (Figure 24) below (23;154;155). The upper left hand curve in the panel describes the diastolic compliance of the left ventricle as it relates transmural pressures (TMP) to ventricular volumes. The lighter curve, as indicated by the arrow, depicts the shift in the compliance curve upon adaptation to the microgravity environment. This shift is due to the stiffness changes that occur with the fluid shifts in microgravity and a relative dehydration of the ventricular interstitial spaces. The stiffness of the left ventricle as a function of the interstitial fluid volume was described by Pogasta (121) and is shown in the curve in the lower part of the panel.

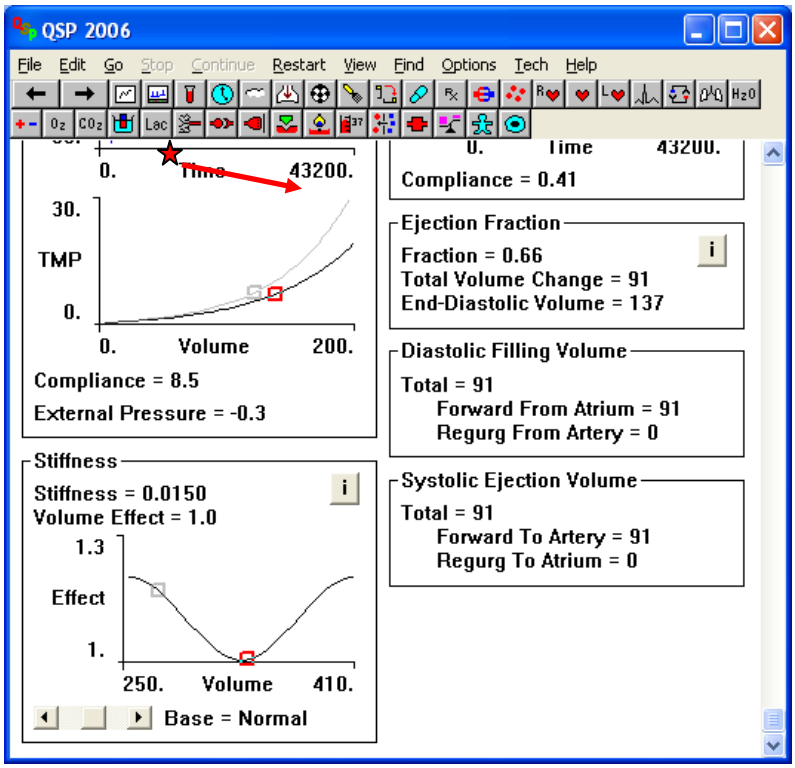

Figure 24. Simulation of microgravity effects on plasma volume and diastolic function.

Simulation studies using the Digital Astronaut Model replicate the findings demonstrated by Levine et al. of a 10% decrement in VO_2max upon reentry (99). This performance validation of the model predictions allows us to extrapolate to what might be expected for VO_2max changes immediately upon entering a Mars or lunar gravitational field (Figures 25 and 26).

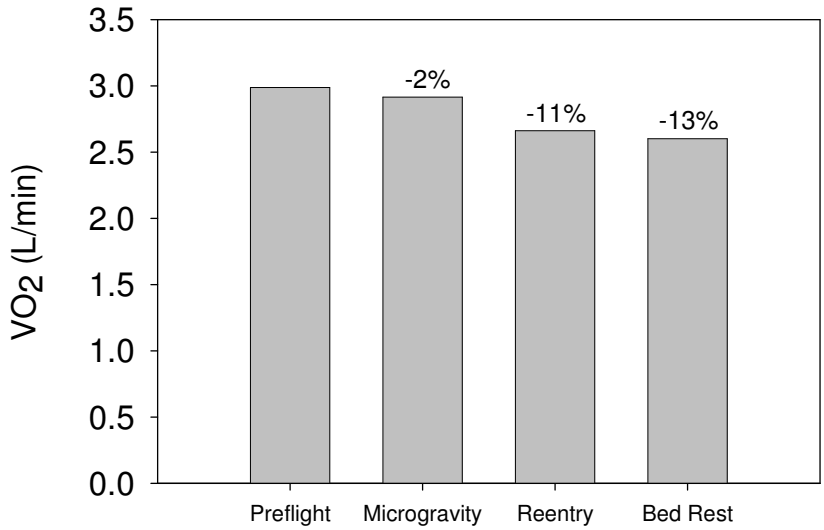

Figure 25. Simulation of the effects of space flight on VO_2max.

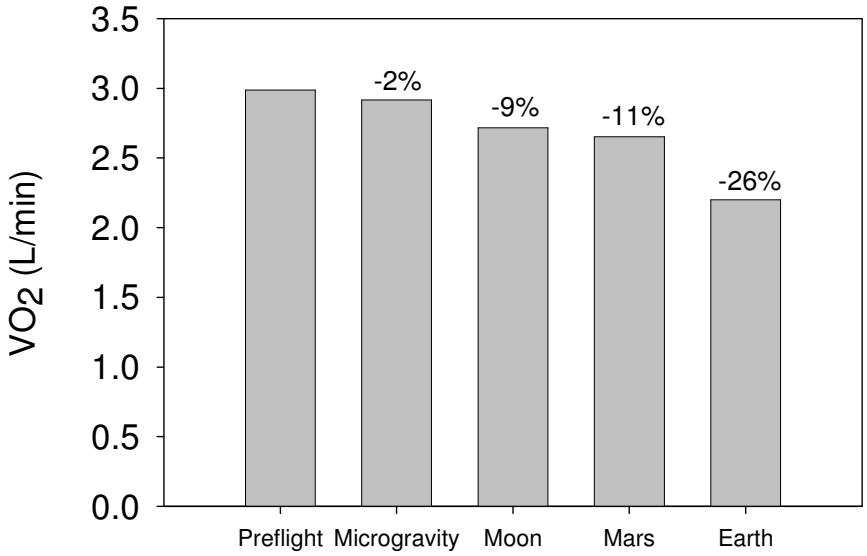

Figure 26. Model prediction of various gravity profiles on VO_2max.

VI. Risk in Context of Exploration Mission Operational Scenarios

The principal risk of reduced aerobic capacity is the inability of crewmembers to perform necessary extravehicular tasks, either in space flight or on the Lunar or Martian surface. During lunar extra vehicular activities (EVA) conducted during the Apollo era, EVA intensity became high, usually manifested by HRs reaching 150-160 beats/min (123). These crewmembers were cautioned to slow their activities when their HRs were observed as high. However, in the future, oxygen uptake associated with building structures or accomplishing more strenuous tasks during longer stays on the moon will likely be as great as or greater than that encountered during Apollo. Furthermore, there is a risk associated with emergency egress upon return to Earth or in a partial-gravity environment (14), where maximum aerobic capacity will be required under conditions that may involve thermal and other stresses.

VII. Gaps

A. Unknown In-flight and Immediate Postflight VO_2max

It is necessary to document the changes in truly measured VO_2max during and following long-duration space flight and lunar habitation missions. Related research questions include:

1) What exercise prescription (modality, frequency, intensity, duration) will be most effective to prevent decreases in aerobic capacity?

2) Are there any non-exercise countermeasures that will aid in the maintenance of aerobic capacity?

3) What is the VO_2max required to perform mission critical tasks, including emergency scenarios?

4) Does VO_2max interact with other factors of fitness (muscle strength, endurance, anaerobic threshold, orthostatic tolerance) to predict critical mission task success?

5) How much effect on VO_2max will the different levels of gravity on the Moon and Mars have?

6) What factors of deconditioning (e.g. plasma volume change, venous return, cardiac function, aerobic enzymes, control of blood flow) are important contributors to the decline in VO_2max as the duration of microgravity exposure continues?

7) How much protection will be afforded by long-time exposure to partial gravity (such as 1/6 G on the moon)?

VIII. Conclusions

Maximum aerobic capacity decreases following short-duration space flight and after bed rest, which is a space flight analogue. Although not directly measured, VO_2max is also believed to be reduced following long-duration space flight based upon observations of elevated HR responses to submaximal exercise loads. Reduced SV, perhaps secondary to lower plasma volume and decreased diastolic filling, is believed to be a major influence on exercise capacity, especially during orthostatic stress. Although no controlled studies of exercise countermeasure effectiveness have been conducted during space flight, data from bed rest studies have demonstrated that countermeasures may attenuate or completely protect aerobic capacity.

Whether exercise capacity is maintained during space flight is unclear, especially during long-duration missions. Understanding these changes is critical when designing a space flight mission and identifying the tasks that a crewmember will be expected to perform. Although performance of activities in microgravity has not been reported specifically to be impaired in space flight operations to date, decreased exercise capacity may decrease the efficiency of work, the intensity at which a crewmember can work, and the duration for which the work can be performed. Crewmembers should maintain a level of fitness that provides additional reserve to be able to successfully react to emergency scenarios. Unfortunately, the required minimum level of fitness can not be fully defined until mission scenarios, critical mission tasks, and suit design are defined. However, acquiring the in-flight data, by direct measurement, that is necessary so planning is not based on assumptions about changes in VO_2max during and after space flight will assist in defining the problem more completely.

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